ADVANCES IN INTERNAL MEDICINE

VOLUME II

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PREFACE

During the years 1942–1945, the editor of *Advances in Internal Medicine* and many of those whose contributions were desirable were in military service, others were doing special work and carrying unusual academic burdens. By the fall of 1944 this unusual way of life had continued long enough to make it seem normal and, at Dr. Steele's request, the editors of this volume undertook to bring together those results of military and civilian experiences which seemed to be the high points of the advances in internal medicine during the war years.

The patience and cooperation of the contributors have been most gratifying. The difficulties of preparation and publication have been trying to publishers, editors, and contributors alike, but to the latter we are especially indebted, as they often found revision necessary by the time their work was submitted for proofreading. These revisions are incorporated in the present volume.

Some of the articles published here deal with investigations of problems peculiarly urgent in time of war. Most of them, as in the collection in Volume I, deal with problems met by surgeons and internists in civilian life. We feel sure that physicians will enjoy and profit by reading both types of contributions, as did the editors when they received the manuscripts.

W. Dock
I. Snapper

New York, N. Y.
February, 1947

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Interpretation of the Ventricular Complex of the Electrocardiogram*

Frank N. Wilson, Francis F. Rosenbaum, and Franklin D. Johnston

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Introduction

So much has been written during the last few years concerning the form of the ventricular complex of the electrocardiogram that it would be impossible, in the space available, to review any considerable fraction of even the more significant articles. We shall, therefore, in the main restrict our attention to problems which can be dealt with on the basis of our own experience and to questions which seem to us of fundamental importance

Although we are concerned here with only one of the two chief purposes served by the electrocardiograph in clinical medicine, it is desirable that the nature of the differences between them be clearly understood. The first is the recognition and differentiation of the disorders which affect the sequence of auricular and ventricular contractions and the time relations between them, the second, the detection of abnormalities which leave these unchanged but alter the relative order in which the different parts of the ordinary ventricular or auricular muscle pass through the various stages of the excitatory and recovery processes.

The disorders first mentioned include the cardiac arrhythmias, the heterogenetic tachycardias, atrioventricular heart block, and the homogenetic ectopic rhythms In by far the greater number of instances these conditions can be easily identified by inspection, palpation, or auscultation of the heart and accessible blood vessels, by fluoroscopic examination of the chest, by recording the venous and arterial pulses simultaneously, or by taking a phonocardiogram In this field, electrocardiography is merely a more convenient and more exact, and not a wholly indispensable diagnostic method Electrocardiography, however, has the very great advantage over

* Many of the observations upon which this article is based were made with the aid of a grant from the Horace H Rackham School of Graduate Studies

chronic heart disease to restrict an individual's activity to a degree much beyond that required to control symptoms When there are no other clues, the patient's age and a series of electrocardiograms taken over a period of sufficient length will often make it possible to decide between the three alternatives listed. In the young, chronic progressive heart disease without physical or roentgenographic signs of cardiac abnormality is rare, and abnormalities of the ventricular complex which persist unchanged over two or three weeks usually represent either residues of a previous acute illness or an unusual cardiac anomaly. The form of the T deflection is very labile and may be altered by a great variety of factors, including the tone of the extrinsic cardiac nerves. Therefore, unless the deviations from the normal are pronounced or distinctive, abnormal T waves are less reliable signs of significant myocardial involvement than abnormal QRS deflections.

Some abnormalities of the ventricular complex are encountered only under very special circumstances, so that their occurrence strongly supports some particular clinical diagnosis. Most of these are distinctive electrocardiographic patterns consisting of specific peculiarities in the outline of both the QRS and T complexes in each of several leads. Examples of such patterns are those that occur in preponderant hypertrophy of one ventricle and those characteristic of myocardial infarction affecting various parts of the ventricular walls They often establish with reasonable certainty a diagnosis which is not inconsistent with the clinical history and other data A diagnosis which, after careful investigation, is not supported by other evidence can seldom be made with confidence on the basis of the electrocardiographic data alone.

This brief discussion points to the conclusion that, from the practical standpoint, the interpretation of the ventricular complex involves (*1*) the accurate differentiation of abnormal complexes from those that are within normal limits, (*2*) the estimation of the reliability of various kinds of deviations from accepted normal standards as evidence of structural or functional myocardial changes, which includes the recognition of electrocardiographic peculiarities that are extracardiac in origin, (*3*) the certain identification of those isolated abnormalities and distinctive patterns that strongly suggest or justify a clinical diagnosis

Some have expressed the view that clinical electrocardiography is an empiric science. It is true that much of the knowledge upon which the practical interpretation of the ventricular complex is based has been acquired through clinical experience and by simple procedures. As such may be mentioned the measurement and statistical analysis of the voltages of the different deflections of a series of presumably normal electrocardio-

other available methods that it makes possible the recognition of ectopic beats on the basis of direct evidence furnished by the form of the ventricular or of the auricular complex

In all of these conditions the electrocardiographic diagnosis is at the same time a clinical diagnosis; there is a nearly perfect temporal correlation between the electrical and the mechanical pulsations of the heart and the former may be considered equivalent to the latter The problems encountered in this branch of electrocardiography are primarily physiologic. No special knowledge of electric phenomena is required for their solution.

Abnormalities of the form of the ventricular complex belong in an entirely different category. Apart from the slight asynchronism in the contraction of the two ventricles in bundle branch block, there is no correlation between them and the character of the cardiac or vascular pulsations. *Since they have no mechanical equivalents they cannot be detected by any means other than an electrocardiographic examination, and there is no reason to suppose that they have any direct bearing upon the ability of the heart to perform its function. Considered as isolated deviations from the normal, distinct from their implications, they have no clinical importance.* A physician may find it desirable to relieve a headache, or to abolish extrasystolic arrhythmia, but inverted T waves do not, of themselves, call for any kind of therapy, or any other interference with the lives of those who display them

These purely electrocardiographic disorders are significant only because of the inferences which they suggest Many of them occur under such a great variety of circumstances that they serve merely as evidence that some cardiac abnormality or anomaly is present, and have an important bearing on the clinical diagnosis only when other objective signs of heart disease are lacking. When this is the case, the physician should attempt to ascertain from the history, and such other data as are available, the probable nature of the etiologic factor or factors involved, whether the cardiac reserve is impaired, and, finally, whether he is dealing with *(a) a structural or functional alteration in the heart which dates from some long-past illness and has no bearing on the patient's future, (b) an acute condition which may be expected to retrogress within a relatively short period, or (c) a chronic disease or degenerative process* which is likely to produce more and more cardiac damage as the years pass The last of these questions is an important one, for if the myocardial disturbance responsible for the electrocardiographic abnormality is acute it is probably wise to confine the patient to his quarters until it subsides, even when there are no complaints referable to the cardiovascular system. On the other hand, it is seldom desirable in

sequence in which the various parts of the cardiac muscle pass through the active state; they find it advantageous to choose, as their potential of reference, that of a point at which the intensity of this field is negligibly small. Members of the second group are of the opinion that the monophasic curve obtained by leading from an injured region on the epicardial surface to a point distant from the heart represents potential variations of the former and not potential variations of the latter. This assumption is considered rank heresy by the first group of investigators, who are accustomed to thinking of an injured region as electrically indifferent. The resulting controversy arises primarily from failure to appreciate that the choice of a reference point for measuring the potential is dictated by the purposes which it is expected to serve, and that the distribution of the action currents produced by isolated filaments of tissue bounded by moist air and the distribution of the action currents of a bulky organ like the heart, particularly when it is surrounded by a large volume of conducting medium, are very different in character (1).

Action Currents of Single Tissue Elements

The electric phenomena that accompany the activation of a single element of excitable tissue have recently been studied by Cole and Curtis (2,3), who carried out their experiments on the large cells of the plant *Nitella* and the giant axon of the squid. In both cases the slender filament of tissue was placed in a narrow trough filled with water and bounded by a dielectric, and was, therefore, surrounded by a very thin layer of conducting medium The voltage across the cell membrane of the axon was measured directly by introducing a long capillary electrode into the axoplasm (4). When the membrane was in the resting or unexcited state, the potential of its outer surface was roughly 50 millivolts above that of its inner surface During excitation this potential difference was momentarily reversed in sign, the outside becoming negative with respect to the inside of the fiber by as much as 108 millivolts It was suggested that the inductance of the membrane might have been responsible for this unexpected change in polarity

It was found that the arrival of the excitatory impulse at a given point is accompanied by a large and sudden decrease in the high impedance and the electromotive force characteristic of the resting membrane. This change is equivalent to the sudden development of a partial short circuit between the outside and the inside of the cell. Current flows from those parts of the positive outer surface of the membrane lying just ahead of the advancing excitation wave through this short-circuited region to the nega-

grams; the classification of abnormal ventricular complexes on a more or less arbitrary basis, and the determination of the incidence of each type recognized in various kinds of heart disease; and the analysis of series of electrocardiograms taken on groups of patients who presented similar symptoms, similar physical signs, or similar structural changes in the heart after death.

Studies of this kind are both valuable and necessary, but it is folly to assert or to imply that they are the sole road to progress in electrocardiographic diagnosis. One of the serious limitations of such empiric methods lies in the likelihood that many of the electrocardiographic phenomena emphasized by the classification adopted will be those that are most conspicuous to the eye, and not those which are most fundamental and most significant. It has frequently been pointed out that "chance favors the prepared mind" and that we see chiefly those things that we are looking for. To arrive at a rational classification of abnormal ventricular complexes and to interpret them on a logical basis requires a clear understanding of the operation of the many factors determining the character of variations in potential at the body surface which are represented by the electrocardiographic deflections. Such an understanding can hardly be acquired without some knowledge of the origin of the cardiac action currents, and the principles which govern their distribution in the body The problems that arise when one attempts to interpret the form of the ventricular complex in accordance with fundamental principles, rather than by the application of a set of rules having no other foundation than that furnished by experience alone, are rather of an electric character than of a physiologic one.

Much confusion concerning the purely electrical elements of our subject has resulted from the different points of view held by two groups of investigators who are confronted by problems of very different kinds. One group is made up chiefly of physiologists interested in the action currents of nerves surrounded, except for a thin film of adherent liquid, by a dielectric, the other, almost exclusively of cardiologists primarily concerned with the interpretation of records of the action currents of the human heart, which is embedded in a relatively extensive volume conductor. The former focus their attention upon the monophasic action potential, or time course of the voltage across the cell membrane during excitation, and consequently regard an injured region, where this voltage does not vary, as the most suitable reference point for the measurement of the potential at the tissue *surface*. The latter are confronted by the problem of ascertaining from the character of the varying electric field associated with the heart beat the

tive cell interior. The sudden change in the impedance of the membrane and the reversal of the direction of flow of the current through it are very nearly simultaneous. The relations, in the case of *Nitella*, between the monophasic action potential, the variations in the conductance of the cell membrane, and the changes in the magnitude and direction of the current flowing through this membrane are illustrated by Figure 1.

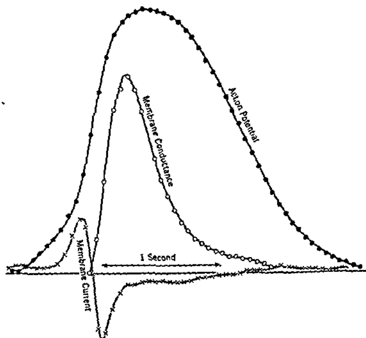


Fig 1 *Membrane conductance, monophasic action potential, and* membrane current *vs.* time after stimulation (after Cole and Curtis, 2). Ordinates are all in arbitrary units Frequency of current used to measure conductance, 0 2 kilocycle

Photographic records obtained by Cole and Curtis (3) in an experiment on the giant axon of the squid are reproduced in Figure 2. In each of the three panels of this figure the variations in the impedance between the electrodes, one on either side of the axon, are represented by the envelope of high frequency current derived from the unbalanced Wheatstone bridge The magnitude of this current is proportional to the decrease of the impedance below its value for the resting axon, for which the bridge was in balance. The action potential, recorded in each instance by leading in the manner indicated in the accompanying diagram, is depicted by a single solid

line. The record of the change in impedance and that of the action potential were superimposed in their proper time relations by a double photographic exposure. The monophasic action potential (Fig. 2A) was recorded by leading from one of the impedance electrodes to one end of the axon which had been rendered inexcitable by the application of a solution of potassium chloride of appropriate strength. Stimuli were applied at the opposite end of the axon through two electrodes at S. The ordinates of this

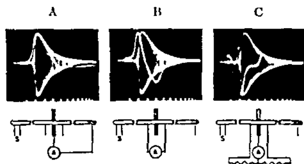


Fig 2 Double exposures of impedance change at 10 kilocycles on each with the action potential in each picture from the circuit shown below it (after Cole and Curtis, 3) A. V, the monophasic action potential, B: V_i, the first derivative or axial current, C V_{ii}, the second derivative or membrane current Time marks at the bottom are 1 millisecond apart

first curve are each proportional to the change in the voltage across the membrane; those of the second (Fig 2B), to the current flowing through the external medium in a direction parallel to the long axis of the cell; and those of the third (Fig 2C), to the density of the current flowing through the membrane from within outward (upward deflection) or in the opposite direction (downward deflection). In mathematical terminology, the third curve is the second derivative of the first and the first derivative of the second

It will be noted that the abrupt decrease in the impedance of the cell membrane, which signals the onset of excitation between the impedance electrodes, coincides with the point of inflection on the rising limb of the monophasic action potential, with the positive peak of the diphasic action potential (Fig 2B), and with the reversal of the direction of the current through the membrane. To ascertain the time of arrival of the excitation or depolarization wave at a given point, either of the last two curves would serve equally well; the first is less suitable for this purpose because the

point of inflection on its ascending limb is difficult to locate accurately. There are no similar indications of the time of arrival of a recovery or repolarization wave. Immediately after its precipitous drop the impedance of the membrane begins to rise, but the return to its resting value is spread over a relatively long interval. In the squid giant axon this process outlasts the monophasic action potential (Fig. 2A); in *Nitella* the opposite appears to be the case (Fig 1). There is no clearly defined point on the curve representing it that uniformly coincides with the second reversal of the membrane current. This second reversal corresponds to the negative peak of the diphasic action potential and the point of inflection on the descending limb of the monophasic action potential. Nor is the second reversal of the membrane current accompanied by a large and sudden movement of the trace comparable to that associated with the first.

Distribution of Action Currents in a Volume Conductor

No experiments comparable to those of Cole and Curtis have been performed upon single cells immersed in a large volume of conducting fluid, but some of the effects of greatly increasing all dimensions of the external medium are predictable. This procedure would decrease the external resistance without altering the impedance of the membrane or the internal resistance of the cell, and would therefore reduce the voltage of the monophasic and diphasic action potentials It would not be expected to have any important effect upon the total current flowing out of or into the cell, nor upon the locations of either the regions of its exit or those of its entrance. In its course outside the tissue, however, this current would no longer be confined to a narrow zone parallel to the long axis of the cell, but would spread out, so that some fraction of it would traverse every part of the extensive external medium

Let us confine our attention for the present to the electric phenomena that accompany excitation, ignoring the complications introduced by the recovery process Electricity flows from points at a higher to points at a lower potential, it follows that the most positive region outside the cell is that part of the membrane's external surface through which current is entering the surrounding medium, and the most negative region is that part of the same surface through which current is leaving it So far as the electric field in this medium is concerned, these two parts of the membrane surface may be regarded as positive and negative electrodes, and, since they are close together and small in extent, as constituting the two poles of a current doublet or dipole (1) Near them the density of the extracellular current is maximal, the lines of current flow are closest together, and the change in

potential per unit of distance is greatest. At a great distance from them, the current density is extremely small, the lines of current flow are very far apart, and the potential is nearly constant. Assuming that the external medium is homogeneous and symmetrically distributed about the tissue, all lines of current flow are normal to the plane perpendicular to the long axis of the cell at the point at which the membrane current reverses its direction. No current flows in this plane; and all parts of it, and also every point in the volume conductor that can be connected to it by a line along which the current density is negligibly small, are at the same potential. The proponents of the "doublet hypothesis" choose this potential as their zero, whereas the proponents of the "negativity hypothesis" assign this value to the potential of the tissue surface in a region which has been injured and is incapable of responding to the excitation process. Throughout this article we shall adhere to the viewpoint and language of the former.

The reversal of the membrane current marks the boundary between the resting and the active tissue Close to this boundary the surface of the former is strongly positive and that of the latter, strongly negative Contrary to what happens when the amount of external fluid is very small, both the positivity of the one and the negativity of the other diminish rapidly as the distance from the place where they meet increases. The curve obtained by leading from a small electrode in contact with the tissue to a distant reference point at zero potential is therefore very much like the diphasic curve which represents the membrane current in Figure 1. To ascertain the time when the excitation wave passes beneath the exploring contact, a lead of this kind is equivalent to that used by Cole and Curtis for recording the second derivative of the monophasic action potential (Fig. 2C) However, no current flows out of the cell at the point which is first to become active, and no current flows into the cell at the point activated last. A lead from the former will therefore yield only the second or negative half, and a lead from the latter, only the first or positive half of the diphasic curve obtained by leading from a point which the excitation wave both approaches and passes. The steep, downward movement which normally joins the positive and negative peaks of this curve begins at the base line in the first case and stops there in the second

Effects Associated with Tissue Injury

If the change produced by excitation in the voltage across the membrane is not the same for every part of the cell, current will flow across the boundaries which define differences in its magnitude until some time during the progress of the recovery process. The characteristic effects of an injured

region upon the action potential are due to its failure to respond normally to excitation (5). In order to avoid complications which have no bearing upon our present theme, we may therefore ignore the current of injury which flows from the uninjured into the adjacent injured area while the former is in the resting state, as well as the depolarization of the latter responsible for it. In other words, we may regard the injured part of the cell as differing from the remainder only as regards the character of its response to excitation. If the electromotive force of the membrane of this part of the cell does not change at all during excitation, or if the change in it is subnormal, current flows out of the injured and into the adjacent uninjured area and this flow lasts from the moment at which the uninjured area is activated until it has been completely, or almost completely, repolarized. This current reverses the direction of its flow through the cell membrane somewhere near the boundary of the injured area. According to our point of view, the point at which this reversal takes place is at zero potential. The injured region is positive with respect to it, and also with respect to a remote electrode, throughout the period during which the normal tissue bordering it remains in the active state.

This applies to a very recent injury (5). Unless the agent which produced the injury continues to act, the injured region is usually sealed off within a short time by the formation of a new cell membrane or polarized surface at its boundary. Thereafter, the damaged tissue has no effect upon the action potential other than that produced by the absence of the electric forces produced by its activation before the injury, and is, in fact, merely a part of the external conducting medium.

Excitation of the Ventricular Muscle

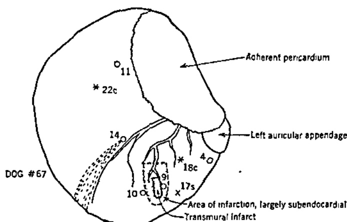
From one point of view, the cardiac ventricles may be regarded as a large, roughly spherical shell open at one end and divided into two parts by a septum. During diastole there is no voltage either across the septum or across the outside walls. Normally, the excitatory impulse reaches the ventricular muscle by way of the His bundle and its branches, the right and the left Purkinje plexus. Excitation of the subendocardial muscle begins at many different points almost simultaneously (6), so that many islands of active tissue, one for each junction between the Purkinje tissue and the ordinary muscle, are quickly formed. As these islands grow they coalesce to form larger islands, until both ventricular cavities are lined almost everywhere except at the valvular orifices by a sheet of active muscle At this stage of

from both sides, there are two such boundaries. The two groups of electric forces associated with the two septal boundaries are opposite in direction and cancel one another more or less completely, so that the voltage across the septum is normally small. The direction of the voltage across the outer walls is such as to make their endocardial surface negative and their epicardial surface positive. The two ventricular cavities are each on the negative side of three of the four boundaries between active and resting muscle, and on the positive side of one of them Both are negative throughout the QRS interval, unless one side of the septum becomes active earlier than the other, in which case the potential of the cavity on the side that is last to become active is initially positive. In some dogs the left side of the septum apparently becomes active first, for the cavity of the right ventricle displays brief initial positivity which is abolished by cutting the left branch of the bundle of His (5). Although both cavities are negative throughout the QRS interval, it must not be supposed that they are necessarily equally negative, or that all points in either are always at the same potential (Fig 3).

Two points separated only by the thickness of the ventricular wall bear substantially the same spatial relations to all the parts of the ventricular muscle other than that which lies between them They lie on opposite sides of a boundary between active and resting muscle, and display a large difference in potential only while this intervening muscle is undergoing activation. When either ventricular cavity is negative, a point on the epicardial surface of the wall which encloses it can be positive only during the period which begins with the excitation of the subjacent subendocardial muscle and terminates with the excitation of the subjacent subepicardial muscle. In leads in which one electrode is placed on an extremity or some part of the body distant from the heart and the other is in contact with the ventricular surface, the end of this period is marked by a very steep deflection similar in character and origin to that which joins the positive and [illegible]

[illegible] type of lead, correctly attributed this rapid movement of the trace to the excitation of the muscle beneath the direct contact, and referred to it as the intrinsic deflection. According to present standards, their tracings were taken upside down, it is now customary to connect the lead wires in such a way that positivity of the exploring electrode produces an upward, instead of a downward, movement in the photographic record (8). When this convention is followed, the intrinsic deflection ordinarily begins at the peak of the R spike and ends either at the apex of the S wave or at the base line (Fig 3).

The adjective "unipolar" may be used to designate leads of the kind under consideration, that is, leads in which the potential variations of the exploring electrode are so much larger than those of its fellow that the latter may be neglected. In unipolar leads from the ventricular surface, the



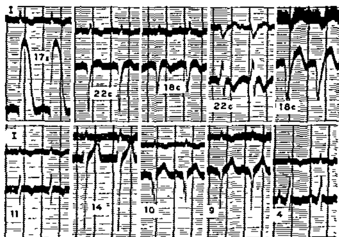


Fig. 3 Unipolar direct leads from dog's heart 19 days after ligation of a branch of anterior descending coronary artery 17s, from an injured region (sharp electrode used), 22c, from cavity of right ventricle, 18c, from cavity of left ventricle, 22c, same as previous curve from this point, but right branch block present, 18c, same as first curve from this point, but right branch block present. 11, from point near base of right ventricle, 14, from point in trabeculated zone, 10, from point at which only deeper layers of muscle were infarcted, 9, from point at which infarct was transmural, 4, from point near base of left ventricle

intrinsic deflection divides the QRS complex into two parts: the deflections preceding it must be ascribed to muscle activated earlier, the deflections following it must be attributed to muscle activated later than that in contact with the exploring electrode. If the muscle upon which this electrode rests is activated last of all, the descent of the intrinsic deflection terminates the QRS complex. If it is not, an S wave is inscribed, for when the voltage across the wall beneath the exploring electrode is abolished by the arrival of the impulse at its epicardial surface the electrode assumes the potential of the adjacent ventricular cavity, which normally remains negative until the end of the QRS interval (5). If the subendocardial muscle subjacent to the exploring electrode is activated later than the subendocardial muscle of the other parts of the ventricular wall, the initial negativity of the adjacent cavity is transmitted through the resting muscle of the wall between it and the electrode, so that a Q deflection results. The ascending limb of the R wave, which immediately precedes the onset of the intrinsic deflection, clearly represents the electric forces associated with the outward spread of the excitation wave through that part of the ventricular wall in contact with the exploring electrode. It should be noted that the height of the R wave is not a good indication of the magnitude of the maximum transmural voltage developed beneath this electrode This voltage is equal to the difference in potential between the endocardial and epicardial surfaces, and this difference is roughly proportional to the amplitude of the intrinsic deflection. The level at which this deflection begins measures the maximum positivity of the latter surface, the level at which it terminates measures the negativity of the former an instant later

Lewis and Rothschild (7), in their extensive experimental study on the order in which the different parts of the ventricular surface are activated, made their measurements from the point at which the intrinsic deflection began. Other investigators have followed their example Since this deflection is of very brief duration, the exact point upon it which coincides with the excitation of the muscle in contact with the exploring electrode is not a matter of great practical importance On the basis of the experiments of Cole and Curtis, however, it is apparent that this point is at the end of the intrinsic deflection and not at its beginning In its spread outward th[illegible]

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lar cavity Nor can this muscle contribute to the negativity of the adjacent cavity, either before excitation of its endocardial or after excitation of its epicardial surface

Were it not for the electric forces produced by the spread of the excitation wave through other regions of ventricular muscle, the activation of a given section of the ventricular wall would be represented, in a unipolar lead from its epicardial surface, by the first phase of a diphasic curve similar to that of Figure 1, that is to say, by an uncomplicated R wave. In that case, the intrinsic deflection would consist of the steep descent beginning at the apex of the R wave and ending at the isoelectric level. Clearly, the situation here is analogous to that previously mentioned, in which the exploring electrode is placed at the point that is activated last. The end of the intrinsic deflection, not its onset, coincides with the excitation of the epicardial surface and the extinction of the transmural voltage. The records actually obtained represent the algebraic sum of (*1*) an R wave of the kind described, written by the muscle between the exploring electrode and the ventricular cavity and (*2*) a downward deflection, representing the potential variations that would occur at the epicardial surface as the result of the excitation of other parts of the ventricular wall alone Whenever it terminates before the QRS interval ends, the intrinsic deflection as a whole is displaced downward by this second deflection, but its termination still represents the activation of the subepicardial muscle beneath the exploring electrode. A Q deflection in leads of the kind under consideration indicates that the adjacent ventricular cavity is negative and that bundle branch conduction on that side is normal The apex of this deflection may occur a trifle after, but cannot occur before, excitation of the subendocardial muscle begins Since the end of the intrinsic deflection coincides with the excitation of the subepicardial muscle, the interval which separates the apex of Q and the end of the intrinsic deflection cannot be less than the time required by the excitation wave to traverse the ventricular wall beneath the exploring electrode. In unipolar direct leads from the ventricular surface (but not necessarily in leads of any other type) this interval is clearly related to the thickness of the muscle between the exploring electrode and the adjacent ventricular cavity, as well as to the speed with which this muscle conducts the excitation wave When Q is absent, the interval from the beginning of R to the end of the intrinsic deflection has the same significance, if it may be assumed that the potential of the adjacent ventricular cavity is initially negative. This assumption may be made only when the QRS interval is normal and the cavity in question is the left (45–47)

It must be constantly borne in mind that the QRS deflections represent the net effects of two sets of electric forces, opposite in sign and both in a constant state of flux The direction in which the potential of any point on the epicardial surface is changing at a given instant depends upon the

relative rate at which these two sets of forces are changing. For an R wave to be inscribed in a unipolar direct lead from a given region it is necessary that the voltage across the wall beneath the exploring electrode increase more rapidly than the negativity of the adjacent ventricular cavity. The presence of a Q deflection may mean that the subjacent endocardial muscle was activated later than the subendocardial muscle of other parts of the ventricular wall, or that the excitation of this muscle produced electric forces which were smaller in magnitude or which increased at a slower rate than the opposing forces.

It may be pointed out that the electric forces of cardiac origin which tend to make one epicardial surface positive tend to make the opposite epicardial surface negative. If there is strong positivity confined to a small region on one surface, one may expect to find a large area of less intense negativity on the other. On the basis of the theorem due to Gauss (9), that the average potential over a spherical surface due to the electric charges inside it is equal to the sum of these charges divided by the radius of the surface, it is clear that the average potential at any instant over the smallest spherical surface that encloses the heart would be zero if the heart were immersed in a homogeneous infinite conductor.

The principles outlined may be utilized to predict the major features of the QRS complex of unipolar direct leads taken under a variety of circumstances. When the predictions based upon them are tested experimentally, one must, of course, anticipate unexpected peculiarities of the form of this complex The endocardial surface of the heart is not smooth but trabeculated. We do not know in detail how the trabeculae and the papillary muscles are activated. Nor do we know how the junctions between the Purkinje system and the ordinary subendocardial muscle are distributed, or how deeply the Purkinje fibers penetrate the septal and free walls of the ventricles The form of the QRS complex is undoubtedly affected by these factors and their variations, as well as by others, but we cannot at present make proper allowances for them.

In unipolar leads from the thinnest parts of the outer ventricular walls the intrinsic deflection normally occurs early in the QRS interval; R is small and narrow, and is followed by a broad and deep S wave Where the ventricular wall is thickest, the intrinsic deflection occurs very late in the QRS interval; R is tall and relatively broad; S is small or absent. Since late activation of the endocardial surface results in late activation of the epicardial surface, a Q wave is almost always followed in normal tracings by a tall R deflection with a late summit

In bundle branch block, the homolateral cavity is initially positive and

finally negative. In epicardial leads from its walls there is no Q deflection; *the R wave consists of two positive components and is bifid, notched, or* broad-topped. One of these components represents the activation of the septum from the contralateral side; the other, the late activation of the free wall of the homolateral ventricle. In similar leads from the contralateral ventrical, a narrow R is followed by a broad S deflection. The curve obtained from a freshly injured area on the epicardial surface is like that obtained from the same area before the injury up to the time when the intrinsic deflection is due If the layer of injured muscle is thin and does not respond at all to the excitation wave, the intrinsic deflection is abolished and the RS-T junction is displaced upward to the level at which this deflection began before the injury. If excitation of the injured muscle occurs and the change in the voltage across the membranes of its fibers produced by this process is subnormal in magnitude, the intrinsic deflection is preserved However, its amplitude is correspondingly reduced and the upward RS-T displacement is smaller.

A lead from the epicardial surface of a transmural infarct, which consists of dead muscle only, is equivalent to a lead from the adjacent ventricular cavity and yields complexes of the same form (10). When only the inner layers of the ventricular wall are infarcted and the excitation wave can spread through them and reach the outer layers by way of fibers that are still excitable, the QRS complex begins with a deep broad Q. The Q wave is followed by a small narrow R; S may or may not be present. This combination is due to a reduction in the magnitude of the forces normally produced by activation of the subendocardial muscle of the region involved A local intraventricular block which delays the excitation of a circumscribed region of the subendocardial muscle gives rise to a very broad Q wave and a tall, late R wave in unipolar leads from the epicardial surface of that region

Recovery Process and Ventricular Gradient

The QRS complex corresponds to the steep slopes of the rising limb of the monophasic action potential, while the T complex corresponds to the more gradual slopes of its descending limb The shape of the T wave is therefore clearly related to the manner in which the voltage across the cell membranes returns to its resting value after excitation The curve representing the membrane current in Figure 1 (page 6) and those obtained by leading from the ventricular surface to a point distant from the heart do not, as we have already indicated, display a second, easily recognizable intrinsic *deflection*, which bears the same relation to the recovery process that the first bears to the excitation process These curves, therefore, cannot tell

us in what sequence the different parts of the epicardial surface pass through any given stage of the repolarization process.

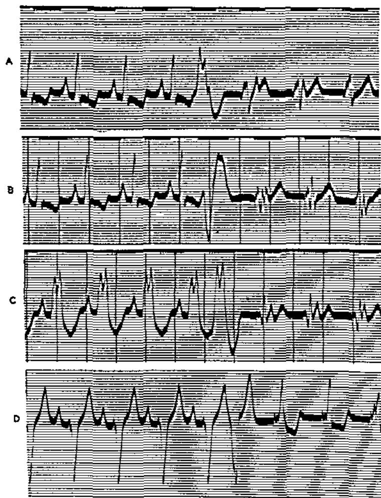


Fig 4 Effect of simultaneous stimulation of right central region and of left apex (11).
A: lead III, normal mechanism,
of left apex, right central region
second after R B· lead III, no
central region and of deeper layers
tive stimulus fell 0 128 second afte
stimulation of right central region and of left apex, right central region recovered first.
D lead II, right bundle branch block, simultaneous stimulation of right central region and of left apex, left apex recovered first

To obtain information bearing on this question, Wilson and Herrmann (11) studied the order in which various parts of the ventricular muscle pass out of the absolutely refractory period. In some of their experiments two points, one on each ventricle, were stimulated simultaneously. The stimuli employed were break induction shocks generated at a rate just below the heart rate, so that each succeeding stimulus fell a fraction of a second later in the cardiac cycle than its predecessor. The form of the ventricular complex of the earliest response made it possible to tell which of the two ventricles becomes excitable first (Fig. 4). In bundle branch block, the epicardial surface of the contralateral ventricle responded to stimuli that coincided with the peak of the T wave, whereas that of the homolateral ventricle did not pass out of the refractory state until the inscription of this deflection was practically complete. When intraventricular conduction was normal, the surface of the central region of the right ventricle passed out of the refractory period earlier than the surface of the left ventricular apex. When the electrode on the left ventricle was thrust into the deeper layers of muscle and that on the right ventricle was left in place, the left ventricle was the first to respond From this the authors concluded that the order in which the ventricular muscle passes out of the refractory period is roughly the same as the order in which it is activated It was found, however, that cooling the epicardial surface, which changed the form of the T wave without altering the form of QRS, greatly increased the duration of the refractory period locally. This observation was considered evidence that the order of excitation and the order of recovery are not necessarily the same

We cannot, then, assume that the time course of the change in transmembranal voltage is everywhere the same, and that excitation and recovery are separated at every point by a constant interval If this were the case, the form of T could be modified only by altering that of the QRS complex, and the net area of QRST would always be zero. If we superimpose two identical curves, each of which represents the monophasic action potential and each of which begins and ends on the X axis, and then shift one of them a short distance to the right or left, they will intersect at a single point. There will then be two narrow areas lying between the two curves and bounded below by the X axis, one to the left and the other to the right of the intersection. It is clear that these two areas must be equal (12) One of them represents the first phase of the diphasic action potential, corresponding in origin to the QRS deflections, and the other the second phase of this potential, corresponding to the T complex. The net area of the diphasic action potential, which represents the potential difference

between two neighboring points, is therefore zero. The ventricular complex of the electrocardiogram represents the sum of all of the potential differences between neighboring points produced by excitation and recovery, and its net area should also be zero.

In this connection we refer again to the curves reproduced in Figures 1 and 2 (pages 6 and 7). Since the diphasic action potential is the first derivative of the monophasic action potential, the latter is the integral of the former; its largest ordinate measures the area of the first phase of the diphasic curve, and its final ordinate, which is zero, measures the net area of both phases. There is a similar relation between the membrane current and its integral, the diphasic action potential This integral is clearly zero, for the total current leaving the cell and the total current reentering it must be equal Of course, this discussion is based on the postulate that the changes in the voltage across the cell membrane occurring at a given point are exactly repeated at points activated later.

The net area of the ventricular deflections is, therefore, a measure of the extent to which these deflections, as a group, represent electric forces due to variations from point to point in the changes in transmembranal voltage associated with excitation and recovery. Presumably, these variations are due to factors that have a purely local influence. In the normal heart, they no doubt comprise natural and inherent differences between the fibers composing the different fractions of the ventricular muscle, or differences in the environmental influences affecting these fibers (e g , differences in innervation, blood supply, or temperature). In the case of the abnormal heart, the factors which might produce similar effects are too numerous to mention

The deflections in the three standard leads at a given instant may be regarded as the projections of a vector upon the three sides of Einthoven's equilateral triangle This vector has only two independent components, one vertical and the other horizontal, it is itself the projection upon the plane of the limb leads of a space vector having the two components mentioned in common with it, and a sagittal component in addition. In the same way the areas of QRS, the areas of T, and the areas of QRST in the three standard leads each determine a vector (12) which may be regarded as the projection of a space vector upon the frontal plane. Bayley (13) has assigned the symbols $\hat{A}_{QRS}$, $\hat{A}_T$, and $\hat{G}$ to the three plane vectors in question, and the symbols $S\hat{A}_{QRS}$, $S\hat{A}_T$, and $S\hat{G}$ to the corresponding space vectors Unfortunately, there is as yet no entirely reliable method of accurately estimating the magnitudes and the directions of the last three.

The areas referred to are those between the trace and the isoelectric

level. Areas which are below this level are considered negative, and those above it, positive. It is convenient to speak of these vectors as the mean electric axis of QRS, the mean electric axis of T, and the ventricular gradient in the frontal plane, or in space, as the case may be. The first represents the time integral of the electric forces produced by ventricular excitation; in a not very precise sense, it gives the average direction taken by the depolarization wave in its course through the ventricular muscle. Similarly, the second represents the forces produced by the recovery process, and gives the inverse of the average direction pursued by the repolarization wave. The third, the vector sum of the other two, represents the electric forces resulting from the deviation of the second wave from the course taken by the first, or more specifically and accurately, from local variations in magnitude and time course of the changes in voltage across the cell membranes during ventricular systole. In the vast majority of cases, these variations involve *solely, or mainly, the time course of* repolarization, sacrificing strict accuracy for brevity, we shall refer to them henceforth as variations in the duration of systole. *The ventricular gradient, then,* points the direction in which the duration of systole diminishes most rapidly (12). However, variations in the duration *of systole not affecting its length,* either at the beginning or at the end of any path pursued by the excitation wave, have no effect upon the ventricular gradient.

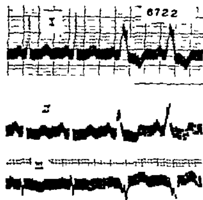


Fig. 5 Intermittent left bundle branch block. For areas of the deflections of both types of complexes, see Table I

To demonstrate that the area of the T wave is determined by two independent factors—*the area of QRS deflections and the ventricular gradient*—and that the latter often remains the same when the forms of the QRS complex and of T change, we reproduce in Table I measurements of an electrocardiogram (Fig. 5) in which QRS complexes characteristic of left *bundle branch block occurred side by side with normal complexes.* The areas of QRS, T, and QRST are given for both types of complexes, and are expressed in microvolt-seconds, figures in parentheses represent values for lead III, obtained by subtracting the figures for lead I from those for lead II. *The differences between these figures and those that they accompany*

represent errors in the measurements as well as actual variations in the ventricular complexes of different cardiac cycles.

TABLE I

TRANSIENT LEFT BUNDLE BRANCH BLOCK. AREAS OF THE VENTRICULAR DEFLECTIONS IN MICROVOLT-SECONDS

Area	Lead I	Lead II	Lead III	Angle α	Manifest magnitude
			Normal complexes		
QRS	19.5	18.3	− 4.3 (−1.2)	27°	21.9
T	0.8	− 9.9	−13.1 (−10.7)	− 86°	11.9
QRST	20.3	8.4	−17.4 (−11.9)	− 6°	20.5
			Abnormal complexes		
QRS	49.7	26.2	−26.5 (−23.5)	2°	49.7
T	−30.7	−19.7	13.1 (11.0)	−171°	31.0
QRST	19.0	6.5	−13.4 (−12.5)	− 10°	19.4

In leads I and II the area of QRST is very nearly the same for both kinds of complexes, while in lead III, the net area of the normal deflections is about 4 microvolt-seconds larger than the net area of the abnormal deflections. This difference is equal to the area of one of the smaller squares that appear on standard electrocardiographic records. By substituting first the normal and then the abnormal values for the same lead in the equation:

$$(\text{area of T}) = (\text{area of QRS})X + Y$$

we can eliminate Y by subtraction and obtain the value of X. By this method we obtain, in the present instance, the following values of X for leads I, II, and III: -1.04, -1.24, -1.18, respectively, with the average for the three figures of -1.15. Considering the possible sources of error, this is close enough to the expected value of -1.0 to indicate clearly that the area of T is determined by the area of QRS and a quantity not appreciably affected by this area, or in other words, by the form of the QRS deflections and the ventricular gradient.

We may conclude that inversion of the T wave in a lead in which this deflection is normally upright may be due to a number of factors: the form of the QRS complex, an unusual or abnormal position of the heart, abnormal local variations in the duration of systole, or to a combination of all three factors. Of course, it has no independent significance when due solely to the first or the second. Although we can only speculate as to their

level. Areas which are below this level are considered negative, and those above it, positive. It is convenient to speak of these vectors as the mean electric axis of QRS, the mean electric axis of T, and the ventricular gradient in the frontal plane, or in space, as the case may be. The first represents the time integral of the electric forces produced by ventricular excitation; in a not very precise sense, it gives the average direction taken by the depolarization wave in its course through the ventricular muscle. Similarly, the second represents the forces produced by the recovery process, and gives the inverse of the average direction pursued by the repolarization wave. *The third, the vector sum of the* other two, represents the electric forces resulting from the deviation of the second wave from the course taken by the first, or more specifically and accurately, from local variations in magnitude and time course of the changes in voltage across the cell membranes during ventricular systole. In the vast majority of cases, these variations involve solely, or mainly, the time course of repolarization, sacrificing strict accuracy for brevity, we shall refer to them henceforth as variations in the duration of systole. The ventricular gradient, then, points the direction in which the duration of systole diminishes most rapidly (12). However, variations in the duration of systole not affecting its length, either at the beginning or at the end of any path pursued by the excitation wave, have no effect upon the ventricular gradient.

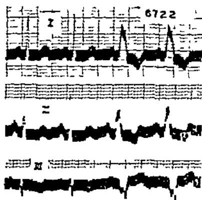


Fig. 5. Intermittent left bundle branch block. For areas of the deflections of both types of complexes, see Table I.

To demonstrate that the area of the T wave is determined by two independent factors—the area of QRS deflections and the ventricular gradient—and that the latter often remains the same when the forms of the QRS complex and of T change, we reproduce in Table I measurements of an electrocardiogram (Fig. 5) in which QRS complexes characteristic of left bundle branch block occurred side by side with normal complexes. The areas of QRS, T, and QRST are given for both types of complexes, and are expressed in microvolt-seconds; figures in parentheses represent values for lead III, obtained by subtracting the figures for lead I from those for lead II. The differences between these figures and those that they accompany

The slope of the first part of the descending limb of the monophasic action potential is the least steep; with a short QRS interval, the electric forces produced by the recovery process are still small when excitation of the ventricular muscle is completed For this reason the RS-T junction is normally near the isoelectric level. When the QRS interval is longer, there is greater overlapping of excitation and recovery and the electric forces due to the latter are large when the QRS interval ends In such cases, the direction of T is usually determined by the large net area of QRS, and the RS-T junction is displaced in a direction opposite to that of the chief QRS deflection. It is not surprising, therefore, that RS-T displacement of this kind is common in bundle branch block and in left ventricular hypertrophy, both of which increase the QRS interval.

There is no valid reason for supposing that RS-T displacement in these conditions is always due to coronary disease. Unlike the RS-T displacement due to acute myocardial ischemia, to very recent myocardial infarction, or to some other type of fresh cardiac injury, that due to overlapping of QRS and T does not change rapidly with time, and is not accompanied by characteristic peculiarities of the RS-T segment. This does not mean that in all cases the two can be distinguished at a glance, or by repeating the electrocardiograms after a short interval.

Ventricular Complex in Indirect Leads

The electric field of the human heart can be studied by means of indirect leads only. In the interpretation of the human electrocardiogram, therefore, we can fully utilize the knowledge gained and the principles established by the use of direct leads from the ventricular surface in animal experiments only if it is possible to show that there are simple relations between the form of the ventricular complex in these leads and its form in leads from the body surface Since the most useful direct leads are of the unipolar variety, this problem is greatly simplified by employing indirect leads which record the potential variations of a single exploring electrode with respect to a reference electrode remaining at or near zero potential throughout the cardiac cycle Since the intensity of the heart's electric field diminishes rapidly as the distance from the heart increases, the first and most important step toward leads of this kind consisted in placing the exploring electrode on the precordium and the reference electrode on one of the extremities (19). Such leads are nearly unipolar, for the potential variations of the central part of the precordium are ordinarily three to five times as large as the potential variations of the parts of the body most distant from the heart A better solution is to replace the reference electrode

origin, the local variations in the length of systole which determine the normal ventricular gradient are not particularly stable. Early investigators, in their attempts to study the cardiac action currents by means of epicardial leads, found the form of the ventricular complex in such leads so variable and so unstable that they virtually abandoned direct in favor of indirect leads. Samoiloff (14), at least, realized that much of the difficulty was due to local cooling and local desiccation of the surface of the exposed heart. In man, drinking a large volume of ice-cold water (15), or, if the chest wall is thin, application of an ice bag to the precordium (16), is sufficient to alter greatly the form of the T wave. Apparently, the change is caused by the lowering of the temperature over a part of the heart's surface. Elevation of the heart rate (17), exertion even when it produces no appreciable cardiac acceleration, and influences reaching the ventricular fibers by way of the cardiac nerves may produce conspicuous changes in the ventricular gradient. Changes of similar magnitude are produced by a variety of drugs, the more pronounced changes being produced by digitalis and its allies. Many intoxications, disorders, and diseases affecting the heart primarily, or only secondarily, may give rise to abnormal T deflections. It has also been demonstrated beyond question that myocardial ischemia of a certain grade, produced by reducing the caliber of one of the coronary arteries, is accompanied by deep inversion of the T wave in direct leads from the surface of the region affected (18). This does not, however, seem to us a sufficient reason for assuming that inverted T waves necessarily have a sinister significance, or that everyone who displays them has something wrong with his coronary arteries. We mention this because those who have occasion to read much of the current electrocardiographic literature may get a contrary impression.

Monophasic action potentials obtained from the amphibian or reptilian heart often have a top that is nearly flat (5). In the electrocardiograms of animals belonging to one of these orders the QRS complex and the T wave are often separated by a long, level segment of the trace which lies on or very close to the base line. The monophasic action potentials obtained from the mammalian heart are more like those shown in Figures 1 and 2A, in which the descending limb begins at the point where the ascending limb ends. Clearly, therefore, repolarization of the muscle that is first to become active begins before the muscle activated later is completely depolarized, and the inscription of the T wave necessarily begins before the QRS interval ends. The last part of the QRS complex is consequently written upon the first part of the T wave as a base line, and the position of what is called the RS-T junction depends upon the direction and slope of the first limb of T

particularly inversion of T in lead V_1, are common to the vast majority of normal precordial electrocardiograms, more or less irrespective of the form of the ventricular complexes of the limb leads. The normal precordial electrocardiogram of the dog closely resembles that of man; apart from their lesser magnitude, the potential variations of a given part of the precordium in this animal are similar in every respect to those of the underlying portions of the anterior ventricular surface. This statement is based

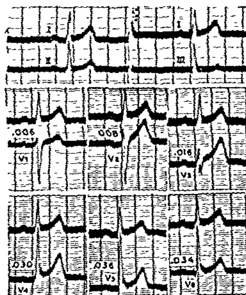


Fig 6 Precordial electrocardiogram of normal subject (25) Decimals on each record give time of onset of intrinsic deflection with reference to the beginning of the QRS interval in lead I, which was taken simultaneously with each precordial lead

upon studies on normal dogs and on animals with the following, experimentally induced, cardiac abnormalities: right bundle branch block, left bundle branch block (Fig. 7), infarction of the anterior wall of the right ventricle, infarction of the posterior wall of the left ventricle, infarction of the anterior wall of the left ventricle, the last plus right branch block, and plus left branch block (23). In the experiments referred to, unipolar precordial leads were taken while the chest was intact, and unipolar direct leads from the anterior ventricular surface after the heart had been exposed. One may justifiably conclude from the results of such experiments that

by a central terminal connected through equal resistances of 5,000 ohms to the three electrodes used in taking the standard limb leads (20). A central terminal so connected is always at the mean potential of the extremity electrodes and there are good reasons for believing that its potential during the cardiac cycle rarely fluctuates through a range of more than 0.3 millivolt (21)

By using such a central terminal, it is possible to take nearly unipolar leads, not only from the central precordium, but also from the axillas, the back, the extremities, and other parts of the body. Unipolar esophageal leads obtained by pairing a small exploring electrode introduced into the esophagus with the central terminal, often give valuable information, but are somewhat inconvenient to use It is the practice in this laboratory to take unipolar leads from each of the six precordial points specified by the Committee of the American Heart Association for the Standardization of Precordial Leads (8), and, in accordance with the recommendations of this committee, to designate these leads by the symbols V_1, V_2, V_3, V_4, V_5, and V_6 The first of the six points is at the right sternal margin in the fourth intercostal space, the second on the left sternal margin at the same level. The remaining points lie on a broken line extending from the second point to the apex beat and thence around the chest at the apical level. When the apex cannot be located, this line is drawn to the intersection of the fifth intercostal space and the midclavicular line, and is continued around the chest at the level of this intersection The third point is midway between the second and the left midclavicular line, the fourth in the midclavicular line, the fifth in the anterior axillary line, and the sixth in the midaxillary line In addition to these six standard leads, we often take a unipolar lead from the tip of the ensiform cartilage (V_E), from the left posterior axillary line (V_7), from the left infrascapular region (V_B), and from the right arm (V_R), left arm (V_L), and left leg (V_F). The last three are taken by the Goldberger (22) technic which increases the size of the deflections by 50 per cent.

The electrocardiogram of a normal subject is reproduced in Figure 6; the standard limb leads and the six standard precordial leads, each taken simultaneously with lead I, are shown The size of the R wave increases steadily from lead V_1 to lead V_4 and decreases from this lead to lead V_6 The peak of this deflection falls early in the QRS interval in leads V_1 and [illegible] The S wave is large in [illegible] . the leads from [illegible] waves are upright in all of the precordial leads These features, with some variations,

in the body is uniquely determined by the potential differences over the epicardial surface that would exist if the heart were completely exposed and surrounded by air. But while it is theoretically possible to predict the potential variations at any point on the body surface if the potential variations of every point on the epicardial surface are known, the converse is not true

A good idea of the general character of the relations between the potential at the surface of the body and the potential at the surface of the heart may be obtained from Poisson's integral (9). It indicates that, if the heart were spherical and embedded in an infinite homogeneous medium of like conductivity, the contribution made by the potential variations of a given element of the epicardial surface to the potential variations of any point outside the heart would be proportional to their magnitude multiplied by the area of the element and divided by the cube of its distance from the point Therefore, the potential variations of a precordial point must represent a mixture of many different components The extent to which the potential variations of the nearest parts of the ventricular surface dominate this mixture depends upon their relative magnitude and the relative size of the area over which similar oscillations in potential take place simultaneously The interpretation of the deflections of unipolar leads from the body surface according to the principles that apply to the interpretation of the ventricular complexes of unipolar direct leads may thus give rise to erroneous conclusions The danger of this error grows rapidly as the distance between the exploring electrode and the epicardium increases. The differentiation of abnormalities or peculiarities in the electrocardiogram that depend upon intracardiac causes from those representing the effect of some extraneous factor (and therefore of no diagnostic importance) is one of the most difficult problems that arise in the interpretation of the ventricular complex

We pass over the artefacts which disfigure such a large percentage of electrocardiograms, and the technical errors that are so common, with the remark that we have seen instances in which an application for life insurance was denied because oscillations in the electrocardiogram due to vibration of the recording apparatus were considered evidence of the presence of auricular fibrillation The interpretation of the form of the ventricular complex is made much more difficult than it would otherwise be by the influence which the position of the heart has upon the character of the ventricular deflections when indirect leads are employed. Rotation of the heart appears to be a far more common cause of puzzling deviations in the electrocardiogram than displacement of this organ as a whole It seems

within certain limits the principles that apply to the interpretation of the ventricular complexes of unipolar direct leads also apply to the interpretation of the ventricular complexes of the unipolar precordial leads We wish to emphasize that ventricular complexes of every type do not necessarily, under all circumstances, have exactly the same significance when they occur

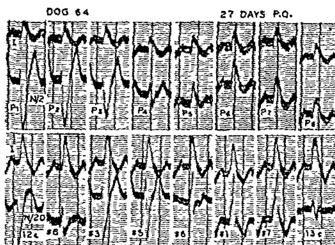


Fig 7 Precordial and direct leads in canine left branch block (25) Tracings taken 27 days after section of left branch of the bundle of His when animal had completely recovered from the operation Precordial leads (P_1 to P_8) taken while chest was intact and with galvanometer at one-half normal sensitivity Direct leads taken with galvanometer at one-twentieth normal sensitivity Points 8, 3, and 5 were on right ventricle, points 6, 1, and 7 on left ventricle Leads from cavity of right ventricle (12c) and cavity of the left (13c) are also reproduced R waves of leads from left side of precordium and surface of left ventricle are made up of two components cavity of left ventricle was initially positive

in a unipolar precordial lead as when they occur in a unipolar direct lead from the ventricular surface. This is very far from being the case

In this connection, we should like to note an observation made nearly a hundred years ago by Helmholtz (24), in his discussion of the distribution of bioelectric currents of the kind then under investigation by E du Bois-Reymond Helmholtz proved that the electric field generated in an inert conductor by bringing it into contact with a tissue carrying such currents is uniquely determined by the differences in potential between any chosen point and all other points on the tissue surface when it is bounded by a dielectric. We may infer that the distribution of the cardiac action currents

The variable relations between the form of the ventricular complex in the unipolar limb leads and its form in the precordial leads encountered in the curves taken on normal subjects were used in a previous article (25) to define six different electrocardiographic positions (Fig 8) of the heart, as follows:

Vertical Position. (a) The ventricular complexes of lead V_L resemble those of leads V_1 and V_2 (b) The ventricular complexes of lead V_F resemble those of leads V_5 and V_6

Semivertical Position. (a) The ventricular complexes of lead V_F resemble the ventricular complexes of leads V_5 and V_6 (b) The QRS deflections of lead V_L are small.

Intermediate Position (a) The ventricular complexes of leads V_L and V_F are similar in form and size and like those of leads V_5 and V_6.

Semihorizontal Position (a) The ventricular complexes of lead V_L resemble those of leads V_5 and V_6 (b) The QRS deflections of lead V_F are small

Horizontal Position. (a) The ventricular complexes of lead V_L resemble those of leads V_5 and V_6 (b) The ventricular complexes of lead V_F resemble those of leads V_1 and V_2.

Indeterminate Position There is no obvious relationship between the ventricular complexes of the limb leads and those of the precordial leads.

The names given to these positions are not intended to imply that the electrocardiographic position of the heart is uniquely determined by its anatomic position, either when this organ is normal or abnormal We are not only aware, but are also certain, that a change in the one is not necessarily accompanied by a change in the other

In the majority of precordial electrocardiograms, the ventricular complexes of the leads from the right side of the precordium and those of the leads from the left side are opposites, as regards the direction of the chief components of the QRS group In normal precordial tracings, the former display small R and deep S waves; in the latter, R is tall and often preceded by a Q deflection, and S is small or absent In one or more leads from the central part of the precordium, the QRS complex has an intermediate form The region which yields complexes of this type may be called the transitional zone The location and the width of this zone are very variable, and it is not always spanned by the standard set of precordial leads It is desirable in such cases to take additional leads from points farther to the right or left, whichever seems indicated Even this procedure may fail if the transitional zone is displaced upward or downward from its usual loca-

to have a greater effect upon the deflections of the limb leads than upon those of the precordial leads, and very often its presence cannot be detected roentgenographically The bearing that the position of the heart has upon the electrocardiogram is demonstrated by the variability of the relations between the form of the ventricular complex in the unipolar limb leads and its form in the six precordial leads. In tracings of normal subjects who

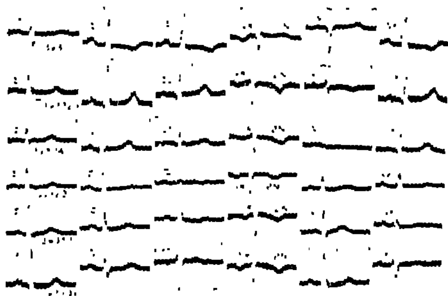


Fig 8 Bipolar (leads I, II, III) and unipolar (leads V_R, V_L, V_F) electrocardiograms of six subjects arranged according to position of mean electric axis of QRS (43) Unipolar limb leads taken with galvanometer at twice normal sensitivity Assuming that QRS deflections of precordial leads, had they been taken, would have been of normal type, heart was in vertical position in the first case, in semivertical position in second and third, in intermediate position in fourth, in semihorizontal position in fifth, and in horizontal position in sixth case

display right axis deviation, the ventricular deflections of lead V_F closely resemble those of leads V_5 and V_6, and the deflections of lead V_L are like those of leads V_1 and V_2 In normal tracings in which the electric axis is shifted to the left, exactly opposite relations occur In both cases the complexes of lead V_F are the inverse of those of lead V_L. These observations suggest that the position of the heart is not the same in the two groups, or that they differ as regards the distribution of the regions of the ventricular surface exhibiting potential variations of the same kind.

Hereafter, we shall speak of leads V_5 and V_6 as if they were always from points to the left of the transitional zone, and of leads V_1 and V_2 as if they were always from points to the right, in order to avoid a constant repetition of the more precise but awkward phraseology of the preceding paragraph.

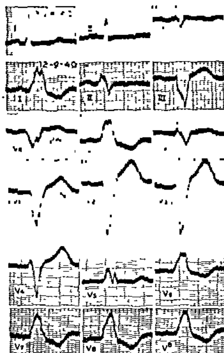


Fig 9 Left bundle branch block, heart in horizontal electrocardiographic position (25). First tracing taken before development of conduction defect. Leads V_B and V^B are both from left back, the second from higher level than the first

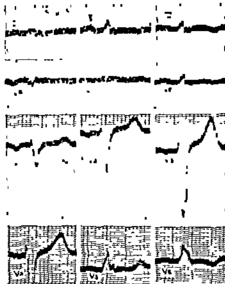


Fig 10. Left bundle branch block; heart in indeterminate position. QRS deflections of limb leads, small and bizarre, those of precordial leads, characteristic of left bundle branch block. Male patient, age 62, history strongly suggestive of coronary thrombosis followed by angina pectoris

In right bundle branch block the precordial electrocardiogram is more or less opposite in form to that of left bundle branch block The leads from the right side of the precordium (V_1, usually V_2, and almost always V_E) ordinarily display a small initial R and a larger late R′ (Fig 11), but these two components may be fused into a single broad, bifid, or flat-topped deflection, as in left branch block The first represents activation of the septum from left to right, and the second, activation of the free wall of the

tion and laterally as well. Obviously, rotation, displacement, or enlargement of the heart can hardly fail to alter the location of the transitional zone, but what other factors may do the same and what changes in its width may mean are still unknown. Since many electrocardiographic diagnoses are based to some extent upon the contrast in form between the ventricular complexes recorded on one side of this zone and those recorded on the other, it is important that it be crossed by the system of leads used. When it is greatly displaced, the interpretation of the precordial electrocardiogram may be uncertain or impossible.

Bundle Branch Block

The principles discussed in preceding sections of this study indicate that bundle branch block can be diagnosed with certainty only when the QRS interval is abnormally long, the epicardial surface of the homolateral ventricle is activated abnormally late, and the cavity of this ventricle is initially positive. In complete bundle branch block the QRS interval measures at least 0.12 second In left branch block it is the cavity of the left ventricle that is initially positive, and there is therefore no Q wave in the complexes of the leads from points to the left of the transitional zone An exception occurs when left bundle branch block is complicated by transseptal infarction (26). The same leads display a broad-topped, bifid, or double R wave, indicating the presence of two components—one due to activation of the septum from right to left, the other, activation of the free wall of the left ventricle from within outward The downstroke ending this R wave represents the intrinsic deflection and occurs very late in the QRS interval In the leads from points to the right of the transitional zone the final QRS deflection is downward and broad. This deflection is usually, but not always, preceded by a small thin R wave with an early peak The form of the ventricular complexes of the limb leads is very variable and depends upon the electrocardiographic position of the heart If this position is horizontal (Fig. 9) or semihorizontal, the ventricular complexes of lead V_L and lead I closely resemble those of the leads from points to the left of the transitional zone If V_F is substituted for V_L in this statement, it holds for the semivertical position When the position is vertical (very rarely the case in left branch block), the complexes of lead V_L and lead I resemble those of the leads from points to the right of the transitional zone, a diagnosis of right branch block is then certain to be made unless precordial leads are taken. When the position is indeterminate, the QRS deflections of the limb leads are, as a rule, small and bizarre (Fig. 10).

ally display a late broad R wave, but resemble the complexes of unipolar leads from the right back much more than those of lead V_1 as regards the relative size and shape of this deflection, as well as in other respects. It also frequently happens that the R deflection of the unipolar limb leads displaying a broad S wave is very much smaller, as compared with the depth of S, than it is in the leads from the left side of the precordium.

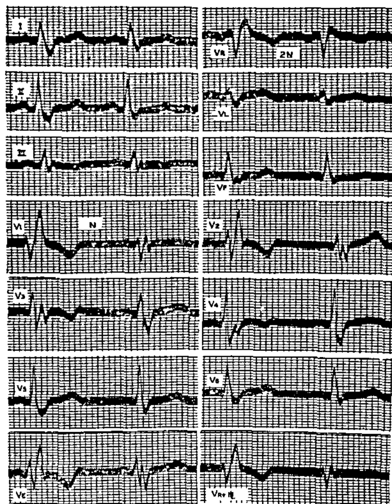


Fig 12. Complete and incomplete right bundle branch block (25) First complex of each pair represents complete block, the second, incomplete Initial part of QRS complex has exactly the same form in both

right ventricle from within outward. The intrinsic deflection begins at the apex of the second component. As the exploring electrode is moved to the left, the first component grows rapidly in size and finally becomes a tall, thin R wave, sometimes preceded by a Q deflection, while the second component rapidly diminishes in size and becomes a broad but often shallow S.

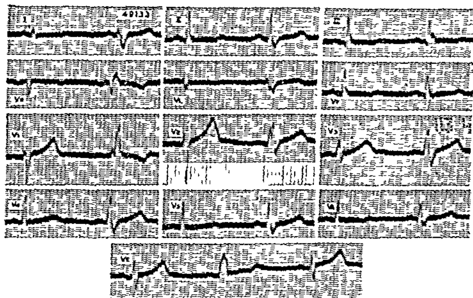


Fig 11. Partial right bundle branch block First complex of each pair represents normal intraventricular conduction; second represents complete right bundle branch block Male patient, age 39, without symptoms or physical signs of heart disease.

In right branch block the wall of the homolateral ventricle is much thinner than that of the contralateral ventricle, whereas in left branch block the reverse is true. This accounts for the contrast between the tall R and broad S *of leads* V_5 *and* V_6 *in the former*, and the small R and deep S of leads V_1 and V_2 in the latter It also accounts for the more distinct separation of the two components of the broad R of the leads from points overlying the homolateral ventricle in the one case than in the other In left branch block the transitional zone is usually much farther to the left than in right branch block; there is evidently a difference between them in the distribution of potential variations of different kinds over the ventricular surface. In the latter, it is rare for the ventricular complexes of either *lead* V_L *or* V_F to resemble those of leads V_1 very closely. The complexes of lead V_R usu-

ally display a late broad R wave, but resemble the complexes of unipolar leads from the right back much more than those of lead V_1 as regards the relative size and shape of this deflection, as well as in other respects. It also frequently happens that the R deflection of the unipolar limb leads displaying a broad S wave is very much smaller, as compared with the depth of S, than it is in the leads from the left side of the precordium.

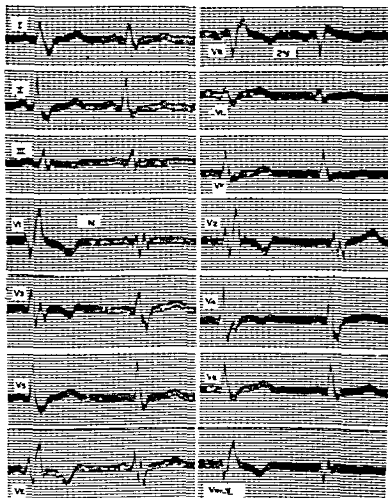


Fig. 12. Complete and incomplete right bundle branch block (25). First complex of each pair represents complete block, the second, incomplete. Initial part of QRS complex has exactly the same form in both.

Incomplete right bundle branch block is common but it can rarely be diagnosed with certainty unless a full set of unipolar precordial leads is taken. The QRS interval usually measures 0 09 to 0 11 second and there is a conspicuous and rather broad S wave in lead I; but the limb leads seldom exhibit peculiarities of the ventricular complex of any real diagnostic value or which can be regarded as definitely abnormal The diagnosis is justifiable when, in addition to a QRS interval of more than 0 08 second, there is a definite secondary R wave in both leads V_1 and V_E. When the R′ wave is very small and confined to the first of these precordial leads,

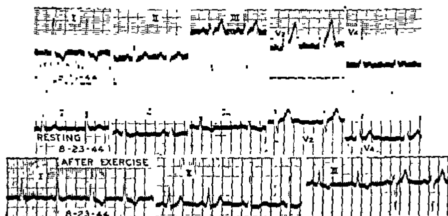


Fig 13 Transient incomplete left bundle branch block Tracing of 8-19-44 suggests presence of left ventricular hypertrophy, that of 8-23-44 is of normal type Transitions from normal to abnormal complexes were recorded Patient in good health, without physical signs suggestive of cardiac pathology. Electrocardiograms taken by Dr John Lavan and reproduced with his permission.

the presence of a conduction defect in the right bundle branch is doubtful In Figure 12 the first complex of each lead represents complete and the second incomplete right branch block The earliest phases of the QRS complex in incomplete bundle branch block must have exactly the same form, in a given lead, as in complete bundle branch block, for in both cases these phases represent the spread of the excitation wave in the contralateral ventricle before it has reached the homolateral ventricle In some cases of mitral stenosis, the precordial electrocardiogram closely resembles that of complete right branch block even though the QRS interval measures no more than 0.10 second Such curves probably represent incomplete right branch block plus right ventricular hypertrophy; the large size of the

R′ wave of lead V_1 in these tracings is attributed to the increased thickness of the free wall of the right ventricle.

The diagnosis of incomplete left branch block is very difficult. The septal and mural components of the R deflection of the leads from points overlying the homolateral ventricle are not separated, as they are in incomplete right branch block, and neither the complexes of the limb leads nor those of the precordial leads can be distinguished from the complexes seen in many cases of left ventricular hypertrophy (Fig 13). Incomplete left branch block can be excluded when there is a Q wave in one or more of the leads from the left side of the precordium, but the absence of Q in these leads is of no help.

The data regarding the effects of ventricular hypertrophy on the form of the electrocardiogram which represent bundle branch block are too few to be of much value, and the problem is a complicated one from the theoretic standpoint Massive hypertrophy of the right ventricle, when combined with right branch block, greatly increases the voltage of the R′ wave in the leads from the right side of the precordium, and tends to diminish the voltage of R and increase that of S in the leads from the left side. Massive right ventricular hypertrophy and left bundle branch block rarely occur together, and the electrocardiographic pattern that corresponds to this combination is still unknown. Massive left ventricular hypertrophy, when combined with left branch block, greatly augments the voltage of the chief QRS deflections and probably increases the QRS interval, but seems to have no other important effects When combined with right branch block, it increases the size of the R deflection in the leads from the left side of the precordium, and probably gives rise to a deeper cleft between the R and R′ waves of the leads from the right side.

Eppinger and Rothberger (27), in 1910, showed that a small cut properly placed on the right side of the upper septum of the dog's heart produces characteristic changes in the ventricular complex of one kind, whereas a similar cut properly placed on the left side of the upper septum produces characteristic changes of a more or less opposite kind The history of bundle branch block in the thirty-five years that have since elapsed has been a story of endless confusion. No sooner is one source of confusion eliminated than another arises A beginner in electrocardiography, after reading the current literature on this subject, will be in doubt as to whether the bundle branches actually exist in the human heart, as to whether it is possible to recognize bundle branch block if it does exist, as to whether right bundle branch block can be distinguished from left and, if it can, whether the differentiation is of any practical importance. He may get the impres-

Incomplete right bundle branch block is common but it can rarely be diagnosed with certainty unless a full set of unipolar precordial leads is taken. The QRS interval usually measures 0.09 to 0.11 second and there is a conspicuous and rather broad S wave in lead I; but the limb leads seldom exhibit peculiarities of the ventricular complex of any real diagnostic value or which can be regarded as definitely abnormal. The diagnosis is justifiable when, in addition to a QRS interval of more than 0.08 second, there is a definite secondary R wave in both leads V_1 and V_E. When the R′ wave is very small and confined to the first of these precordial leads,

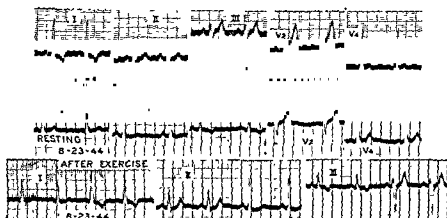


Fig. 13. Transient incomplete left bundle branch block. Tracing of 8-19-44 suggests presence of left ventricular hypertrophy, that of 8-23-44 is of normal type. Transitions from normal to abnormal complexes were recorded. Patient in good health, without physical signs suggestive of cardiac pathology. Electrocardiograms taken by Dr John Lavan and reproduced with his permission

the presence of a conduction defect in the right bundle branch is doubtful. In Figure 12 the first complex of each lead represents complete and the second incomplete right branch block. The earliest phases of the QRS complex in incomplete bundle branch block must have exactly the same form, in a given lead, as in complete bundle branch block, for in both cases these phases represent the spread of the excitation wave in the contralateral ventricle before it has reached the homolateral ventricle. In some cases of mitral stenosis, the precordial electrocardiogram closely resembles that of complete right branch block even though the QRS interval measures no more than 0.10 second. Such curves probably represent incomplete right branch block plus right ventricular hypertrophy; the large size of the

arborization block, a general functional depression or degeneration of the Purkinje tissue in its entirety, and perhaps still other types of lesions.

Ventricular Hypertrophy

Normally, the left ventricle is more massive and has a much thicker wall than the right. This natural difference between the two chambers is greatly increased in left ventricular hypertrophy; in right ventricular hypertrophy it is either diminished or reversed. It is not surprising, therefore, that in the former the precordial electrocardiogram exhibits in an exaggerated form some of the characteristics of normal tracings. The normally small R waves of leads V_1 and V_2 are even smaller, and the normally large S waves of these leads, still larger. In leads V_5 and V_6 the peak of R is abnormally late and this deflection is abnormally tall (Fig 14). It is preceded by a Q wave in more than half the cases, and is very often followed by an inverted T deflection. The QRS interval frequently measures 0.10 or 0.11 and sometimes even 0.12 second. In pronounced right ventricular hypertrophy, on the other hand, the precordial electrocardiogram is of a more or less opposite kind. Abnormally large R waves with a late peak, and frequently Q waves, inverted T waves, or both occur in the leads from the right side of the precordium (leads V_1, V_{E}, and often V_2). In the leads from the left side, R is often unusually small, its peak sometimes unusually early, and Q is absent. The QRS interval ... much greater than normal, and the chief ... as large as in left ventricular hypertrophy

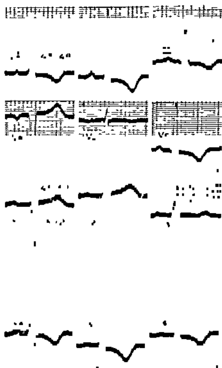


Fig 14. Left ventricular hypertrophy; heart in semivertical position (25). R deflections of leads I, II, V_F, V_4, V_5, and V_6 abnormally tall and followed by inverted T waves, QRS interval slightly increased, no axis deviation. Female patient, age 50 years, with hypertensive heart disease

sion that the presence of bundle branch block means a life expectancy of something like two or three years, or that it is synonomous with the existence of "coronary disease."

These problems cannot be discussed at length here, and we must content ourselves with a few disconnected remarks. (*1*) There are certainly in the United States some thousands, if not tens of thousands, of men, working every day and engaging in various kinds of strenuous activity, who show no symptoms but who, nevertheless, would display bundle branch block, right or left, complete or incomplete, if their electrocardiograms were taken. There is every reason to suppose that the vast majority of those who do not have hypertension and exhibit no physical signs pointing to heart disease may expect to live about as long as the average man of like age (*2*) Most of our present knowledge of the form of the ventricular complex has been acquired through the study of bundle branch block. The problems which the electrocardiograms supposedly representing this abnormality originally presented were of a kind impossible to solve by the empiric approach It was necessary to solve the more urgent of these or abandon hope of understanding the form of the ventricular complex. (*3*) The bundle branches may or may not exist as sharply differentiated muscular structures in the histologic sense, but they surely exist as distinct entities in the physiologic sense and play an important role in the transmission to the ventricular muscle of impulses that originate in the auricles. The failure of both to function produces complete atrioventricular block Each performs like a single strand of tissue, for in the same record ventricular complexes of the normal type and complexes characteristic of bundle branch block may alternate (Fig. 11, page 32) The occurrence of this phenomenon also proves, *beyond reasonable doubt, that bundle branch* block is in no way dependent upon the condition of the ordinary ventricular muscle as a whole. (*4*) While it is true that right and left branch block occur with almost equal frequency in some types of heart disease, it is *by no means true of all Right branch block, for example,* is common in pulmonary embolism, left branch block does not occur in this condition. We cannot tell whether the differentiation of right from left branch block is of importance from a practical standpoint until we can diagnose both with something like absolute certainty. (*5*) There are numerous types of abnormal electrocardiograms which are still being attributed to right or left bundle branch block, although they almost certainly represent some-

[illegible] left ventricular

branches of in the ventricular [illegible]

no means uncommon. Left axis deviation (heart in the vertical position) is theoretically possible, but it is apparently rare.

In preponderant hypertrophy involving either ventricle, the T waves of the leads in which the largest R waves occur are very commonly inverted. How often these abnormal T waves are due chiefly or entirely to the large areas of the R waves which they follow, and how often to an abnormal ventricular gradient has not yet been finally determined. Like several other observers we have seen a good many cases of hypertensive heart disease in

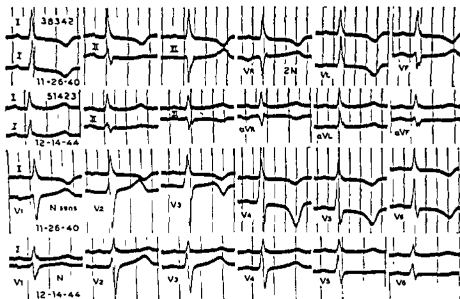


Fig 16. Electrocardiograms before and after splanchnicectomy performed on 12-4-40 Male patient, age 38, symptoms of seven years' duration; blood pressure, 245/145 mm Hg at time of operation, on 12-14-44, blood pressure, 124/86 mm. Hg

which the inverted T waves of lead I, or leads I and II, and of the leads from the left side of the precordium became and remained normal after splanchnicectomy (Fig. 16) Sometimes, but not always, this phenomenon is accompanied by an obvious decrease in the heights and areas of the R waves in the same leads The term "ventricular strain" has been used for the combination of the QRS and T wave changes in question We are not certain as to the exact meaning of this expression, or as to whether it has been used in exactly the same sense by all writers It may be used by some merely as a substitute for a longer, but more descriptive, name for the electrocardiographic abnormalities mentioned, or to indicate only that the

in location, but is frequently to the right of its usual position, whereas in left ventricular hypertrophy it is almost always displaced to the left.

In left ventricular hypertrophy, the limb leads ordinarily display left axis deviation (heart in the horizontal or semihorizontal electrocardiographic position), or no axis deviation with abnormally large R waves

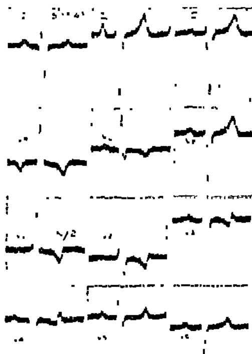


Fig 15. Electrocardiogram of Negro boy, aged 11, with congenital heart disease, probably tetralogy of Fallot Precordial curves are characteristic of massive hypertrophy of right ventricle, large S waves and small or relatively small R waves in all of standard limb leads

(heart in the semivertical position) as in Figure 14. The last is more common when the patient is youthful In rare instances right axis deviation occurs (heart in the vertical position) In right ventricular hypertrophy, the limb leads usually show right axis deviation, but curves characterized by small R waves and large S waves in leads I, II, and III (Fig 15) are by

is no definite indication of an appreciable delay in the activation of any large part of the subendocardial muscle.

In right ventricular hypertrophy, Q waves occur in the leads from the right side of the precordium, in which they are normally absent; they may be due both in right and in left ventricular hypertrophy to a decreased density of the junctions between Purkinje and ordinary muscle in certain areas, as a result of dilatation of the chamber chiefly affected The increased thickness of the free wall of the hypertrophied ventricle may enable it to produce electric forces which abnormally overbalance, as well as outlast, the opposing forces developed in the septum and in the free wall of the more normal chamber. Dilatation of this ventricle may increase the epicardial area over which potential variations of a certain kind occur simultaneously, thereby increasing the size of the contribution made by such potential variations to the form of the ventricular complex in leads from points on neighboring parts of the body surface. It is also possible that the increase in the size of the muscle fibers may increase the voltage generated by them on excitation, by decreasing the internal resistance without altering the external Which of these factors is mainly responsible for the increased size of the chief deflections in indirect leads is at present not clear The reduction in size of the R waves and the absence of Q waves in the leads from the left side of the precordium in massive hypertrophy of the right ventricle, and the absence of R waves in the leads from the right side of the precordium in massive hypertrophy of the left ventricle, are apparently indirect effects produced by the factors responsible for the increased incidence of Q waves and the abnormally tall R waves of the leads from the opposite side of the precordium in each case

In long-standing hypertension, broad and slurred or notched QRS complexes may eventually appear This has led to the belief that in preponderant left ventricular hypertrophy left bundle branch block often develops gradually It is probable that complexes of the kind in question represent faulty conduction in the specialized ventricular tissues, or in the ventricular walls We are confident that in the vast majority of instances they do not represent left bundle branch block, either complete or incomplete We also doubt that hypertrophy which increases the masses of the two ventricles proportionately can, as yet, be distinguished with any certainty from preponderant hypertrophy of the left ventricle on the basis of the electrocardiographic abnormalities present.

Myocardial Infarction

It has been shown in animal experiments that when the caliber of a

cardiac disorder which usually gives rise to them is present. Our main objection to its use is that the word "strain" is a common one with definite connotations, and when the term "ventricular strain" is employed it can hardly fail to convey the impression not only that the heart is carrying a heavy burden, but that this burden is one that it cannot long support. We have, however, seen striking electrocardiographic abnormalities of the kind that are so common in hypertensive heart disease persist unchanged over a ten year period. So far as we are aware, neither hypertrophy of the left ventricle, dilatation of this chamber, myocardial ischemia, impending ventricular failure, nor any particular combination of these has been conclusively shown to be the cause, or not the cause, of the inverted T waves in tracings of this kind. We speak here of all types of inverted T waves that occur with great frequency in hypertensive heart disease, and without any reservation with respect to the position of the RS-T junction or the shape of the RS-T segment, so long as both persist without material change over a considerable period of time.

An increase in the voltage of the QRS deflections occurs both in preponderant left and in preponderant right ventricular hypertrophy, but it is especially pronounced in the former. The cause of this voltage increase and some of the other electrocardiographic phenomena that occur in preponderant hypertrophy of one ventricle is not altogether clear. It is easy to understand that hypertrophy of the left ventricle must increase the amount of muscle activated in one direction and hypertrophy of the right ventricle, the amount of muscle activated in the opposite direction, and consequently that the effect of the former upon the net area of the QRS complex must be the opposite of that produced by the latter. It is more difficult to see why the change in this area should be brought about in part by an increase in the height of the chief QRS deflections rather than by a change in their breadth alone. Preponderant hypertrophy usually involves an increase in the thickness of the septal and free walls, in the total epicardial area, and in the size of the fibers of the chamber affected. It may also diminish the density of the junctions between Purkinje tissue and subendocardial muscle, and increase the length of the paths traversed by the excitation wave on its way to some of these junctions.

We think that the last is unlikely and believe that the lengthened QRS interval in preponderant hypertrophy of the left ventricle is due chiefly, if not entirely, to the increased thickness of the outside wall of this chamber. Although Q waves are perhaps more frequent, and possibly deeper or wider, in the leads from the left side of the precordium when the left ventricle is enlarged than when the heart is normal, in the vast majority of cases there

form, even when it cannot be easily distinguished from it by a single observation. It is associated with ventricular aneurysm more often than one might expect on the basis of what is known concerning the individual frequencies of the two phenomena. This probably only means that infarcts of the kind which produce the one are in some respects like those that lead to the other.

In unipolar direct leads from a part of the ventricular wall deprived of its blood supply, a prominent Q wave makes its appearance while the RS-T displacement is still pronounced, and as the displacement decreases the Q wave becomes broader and much deeper. As we have mentioned on page 13, this deflection represents the transmission to the epicardial surface of the initial negativity of the adjacent ventricular cavity. When the infarct is transmural and contains little or no living muscle, the ventricular complexes of unipolar epicardial leads and those of unipolar cavity leads are practically identical, and the QRS group of these complexes is represented by a deep QS deflection. Ordinarily, some muscle escapes destruction. If it is small in amount, the QS deflection displays a notch due to the superimposition of an embryonic R wave upon its descending or ascending limb. When, as often happens, the outer layers of muscle remain relatively intact, an abnormally deep Q is followed by an R wave of subnormal size. Since this combination is not as a rule accompanied by an appreciable increase in the QRS interval it must mean that the excitatory impulse reaches the endocardial surface of the infarct at the normal time, and spreads to the outer layers of muscle with the normal speed by way of living and excitable fibers of the more seriously involved deeper layers. The ischemia of the outer layers of muscle is often of a grade which increases the duration of their systole and thus gives rise to deeply inverted T waves. There are, however, cases of old infarction of the human heart in which precordial or esophageal leads exhibit wide QRS complexes, up to 0.12 second or more in duration, consisting of a very broad Q followed by a very late R deflection. This combination indicates that the activation of the subendocardial muscle has been delayed by local involvement of the Purkinje plexus, or that the transmission of the cardiac impulse through this muscle is abnormally slow.

Myocardial infarction gives rise to a sequence of changes in the form of the ventricular complexes of unipolar leads from the body surface similar to that which it produces in epicardial leads (Fig. 17). The earliest and most transient of the phenomena regularly observed is RS-T displacement. It shows a pronounced tendency to regress and may be conspicuous for only a few hours, but frequently persists for a week or longer. In our ex-

coronary artery is gradually reduced the first change in the ventricular complexes of unipolar direct leads from the epicardial surface of the affected region is the development of deep, sharply inverted T deflections; these rapidly retrogress when the normal circulation is restored. A greater grade of ischemia gives rise to upward displacement of the RS-T junction and segment; this change also is reversible if not maintained too long. Prolonged high-grade obstruction of a coronary artery results in fatal injury to the muscle irrigated by it which is not protected by an adequate collateral blood supply. The damage to the deeper layers of muscle is usually, although apparently not always (28), more severe and widespread than the damage to the more superficial parts of the ventricular wall. Nevertheless, a thin layer just beneath the endocardium and the Purkinje plexus (which lies mainly in this layer) almost always survives, either because of the diffusion of oxygen from the ventricular cavity, or because of a collateral flow of blood through the thebesian veins or the anastomoses of the subendocardial arteriolar plexus formed by the terminal branches of the arteries penetrating the ventricular wall nearly perpendicular to its outer surface This inner lamina of uninjured or less seriously injured muscle may account for the usually upward direction of the RS-T displacement in unipolar leads from the epicardial surface, for both theoretic considerations and the experimental evidence available (29) indicate that injuries which are more extensive on the inner than on the outer surface of the ventricular wall depress rather than elevate the RS-T junction and segment in leads of this kind Observations by Bayley (30) strongly support the belief that the direction of the RS-T displacement associated with attacks of anginal pain and with myocardial infarction is sometimes "against the rule," and that displacement of this sort may represent the effects produced by spasm of the arteriolar plexus mentioned

The RS-T displacement associated with infarction is evidently due to the presence of nonpolarizable boundaries which define differences in magnitude of change in transmembranal voltage produced by the excitatory process It shows a pronounced tendency to regress and disappear, either because these boundaries are obliterated by the recovery or death of the injured muscle, or because they become polarizable through a kind of demarcation process. When RS-T displacement persists over a long period without any change in magnitude or form of the RS-T segment, it can hardly be the result of boundaries of the kind referred to, it should be attributed to some other cause, such as overlapping of the QRS and T complexes More or less permanent RS-T displacement does sometimes occur in myocardial infarction, but it can hardly have the same significance as the transient

appear, but residual inversion of the T wave may persist indefinitely. More permanent abnormalities of the T deflection do not, as a rule, have a very distinctive character, nor are they necessarily always due to the persistence of myocardial ischemia. The effect which an infarct has upon the form of the ventricular complexes of a unipolar lead from a given point on the body surface is roughly proportional to the magnitude of the solid angle which its epicardial surface subtends at that point. This angle is measured by the area which lies inside the cone defined by lines drawn from the given point to every point of the boundary of the epicardial surface of the infarct, and forms a part of the spherical surface of unit radius of which the given point is the center. The RS-T displacement recorded is upward if an observer looking through this cone from its apex would see the epicardial surface of the infarct, if he would see its opposite surface, the RS-T displacement is downward.

In indirect unipolar leads the ventricular complex represents potential variations from all parts of the heart's surface, mixed in varying proportions depending upon factors already discussed Pronounced RS-T displacement, abnormally large Q waves, and deeply inverted T waves are not, and clearly cannot be, simultaneously present in a single direct lead. But in an indirect lead the ventricular complex may represent a combination of all three In this combination, RS-T displacement tends to obscure the other components and particularly the sharp inversion of the T wave. In the earlier stages of infarction the surface area of the living subepicardial muscle ischemic enough to give rise to RS-T displacement is evidently much larger than that of the living subepicardial muscle ischemic only to the degree that produces sharply inverted T waves. This relation changes rapidly and is ordinarily soon reversed. When the surface areas specified are of approximately the same size, there may be no distinctive modifications of the T complex in indirect leads, the effect of the one canceling that of the other This is one, though not necessarily the sole, cause of the delayed appearance of evidence of infarction in the electrocardiogram The signs of infarction probably appear late in other cases because the lesion is at first small, or is unfavorably located with reference to the leads employed, and subsequently expands or extends.

Essentially, the changes in the ventricular complex produced by myocardial infarction are always the same, but the size and location of the lesion and the position of the heart in the thorax determine the leads in which these changes occur The electrocardiographic patterns that may be considered diagnostic of myocardial infarction have been classified on the basis of the leads in which characteristic modifications of both the QRS

perience, unusually prolonged RS-T displacement has been an unfavorable omen. If it increases again after it has definitely waned, the reason *may lie in an extension of the infarct or in the development of pericarditis.* The abnormally large Q waves, or QS deflections, also occur early and may

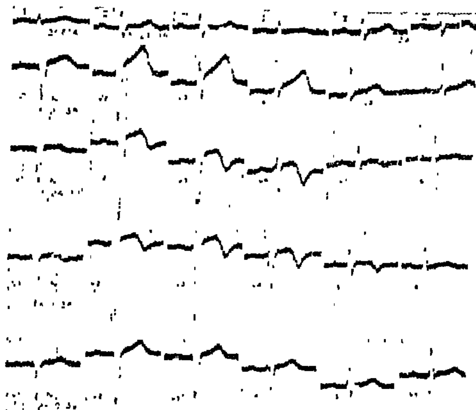


Fig 17 Serial electrocardiograms in a case of anteroseptal infarction (25). First tracing taken about two hours after coronary accident Nine months later T waves no longer abnormal and only QRS changes remained Note delay in the appearance of these changes and absence of diagnostic modifications of ventricular complexes of limb leads

be permanent. Very often, with time, these changes in the QRS complex become less distinctive, and the *number of precordial leads which exhibit* them becomes smaller Terminal inversion of the T complex may appear almost as early as the QRS changes, but the inverted T waves do not usually reach their full development for anywhere from ten days to three weeks They regress over a period of weeks or months and often completely dis-

(*g*) *Postero-Inferior or Posteroseptal Infarction.* This is relatively uncommon. It differs from (*e*) in these particulars: there are abnormally large Q waves and upward RS-T displacement or sharply inverted T waves in lead V_E and sometimes in lead V_1.

(*h*) *High Posterolateral Infarction* This closely resembles (*d*) but the changes in the standard leads from the right side of the precordium are like

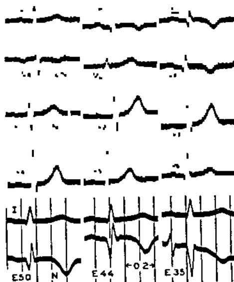


Fig 18 Posterior infarction (25) Note characteristic changes in the QRS and T complexes of leads II, III, and V_F, and similar changes in leads from ventricular levels of esophagus Esophageal leads labeled E followed by a number giving the distance (in centimeters) of exploring electrode from nares

those often seen in posterior infarction, and abnormal Q waves and inverted T waves occur in leads from the upper left axilla and upper left back.

The primary object of this rather elaborate classification is not to make the diagnosis of the location of the infarcted muscle more precise, since there is little reason to suppose that the exact location of the parts of the ventricular walls involved has any special clinical significance Its main purpose is to show that in order to obtain unequivocal electrocardiographic evidence of infarction it may be necessary to take, when the occasion demands it, not only the standard limb leads and the full set of standard pre-

deflections and the T complex appear, and have been given names indicative of the parts of the ventricular wall known, or thought, to be involved (25). This classification includes only those patterns that are encountered repeatedly. Characteristic changes in the QRS complex alone, or in the T complex alone, may be strongly suggestive of infarction, but seldom establish this diagnosis beyond question in the absence of other supporting evidence. This may be wholly clinical, or may be furnished in part by the sequence of electrocardiographic phenomena, rarely observed in any other condition, which we have already described. The more common of the diagnostic patterns seen are the following.

(a) *Anteroseptal Infarction.* Characteristic changes in both the QRS group and the T complex are confined to one or more of the first four of the standard precordial leads. Leads V_5, V_6, V_L, and I may show more or less distinctive changes in the T complex but do not exhibit typical changes in QRS. There are sometimes prominent Q waves in leads II and III.

(b) *Anterolateral Infarction* The diagnostic changes are in lead V_5, in leads V_4, V_5, and V_6, or in some such combination of the standard precordial leads which does not include the leads from the right side of the precordium. There are similar changes in lead I and lead V_L.

(c) *Extensive Anterior Infarction.* This may be regarded as a combination of (a) and (b). Leads I and V_L and all the standard precordial leads except V_1, show typical alterations in both the QRS and the T complex.

(d) *High Anterolateral Infarction.* There are diagnostic changes in lead I and lead V_L, and in unipolar leads from parts of the left side of the precordium or of the anterior surface of the left side of the chest that are nearer the left shoulder than those from which leads V_4, V_5, and V_6 are taken. The complexes of some of the standard leads from the left side of the precordium are abnormal but show much less pronounced changes than those exhibited by the leads mentioned

(e) *Plain Posterior Infarction.* There are diagnostic changes in the complexes of lead V_F and in both leads II and III, or in one or the other There are similar changes in leads from the ventricular levels of the esophagus (points at least 10 cm. below that which yields the largest auricular deflections). The standard precordial leads usually show downward RS-T displacement in the earliest stages of infarction, and in the later stages often show abnormally large R and T waves in the leads from the right side of the precordium (Fig 18).

(f) *Posterolateral Infarction* This differs from (e) only in these respects there are typical changes in the QRS and T complex of lead V_4 or leads V_4 and V_6 and, usually, inverted T waves in lead I.

(*g*) *Postero-Inferior or Posteroseptal Infarction.* This is relatively uncommon It differs from (*e*) in these particulars: there are abnormally large Q waves and upward RS-T displacement or sharply inverted T waves in lead V_E and sometimes in lead V_1.

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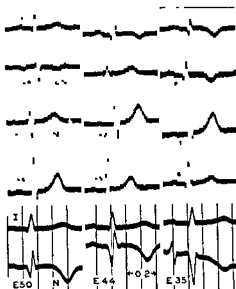


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cordial leads, but other unipolar leads as well. It must not be supposed that the electrocardiographic changes produced by every infarct will correspond exactly to those listed under one of the captions employed. The point is that the most characteristic changes sometimes occur in the leads from the right side of the precordium, sometimes in the leads from the extreme left side of the precordium, sometimes in lead V_E or in precordial leads taken at a higher level than those that are standard, sometimes in the standard limb leads, sometimes in the unipolar limb leads, and sometimes in the esophageal leads.

Myocardial Infarction Complicated by Bundle Branch Block or *Arborization Block*

The electrocardiographic changes in myocardial infarction are apparently almost always due mainly to involvement of the wall of the left ventricle or the septum. In right branch block the cavity of the left ventricle is negative at the beginning of the QRS interval; this negativity is transmitted to the epicardial surface of the infarct or to the cavity of the right ventricle *if the septum is involved. In left bundle branch block the cavity of the* left ventricle is positive at the beginning of the QRS interval, unless the right side of the septum is infarcted, and this positivity is transmitted to *the surface of the infarct*

In anterior infarction plus right bundle branch block there is usually no small initial R wave in the leads from the right side of the precordium, so that these leads exhibit a prominent Q wave followed by the tall, late R deflection due to delayed activation of the free wall of the right ventricle (Fig. 19). Leads from points farther to the left show large Q waves or QS waves Characteristic changes in the T complex are usually also present if the infarct is not an old one. Changes diagnostic of infarction are not, as a rule, present in the limb leads In posterior infarction plus right bundle branch block there are, in the majority of cases, large Q waves in leads II and III and in lead V_F In this case also the changes in QRS are accompanied by more or less typical modifications of the T complex if the infarct is not too old The QRS complexes of the leads from the right side of the precordium are like those seen in uncomplicated *right branch block*

When left bundle branch block is present infarction of the free wall of the left ventricle does not give rise to characteristic *modifications of the* QRS complex in any lead The reason for this is obvious *The cavity of* the left ventricle is positive at the beginning of the QRS interval and this positivity is transmitted through the infarcted region to its epicardial surface and to *adjacent parts of the body.* The infarct, therefore, cannot pro-

duce abnormally large Q waves or QS deflections Unipolar leads from parts of the precordium overlying an anterior infarct may exhibit QRS complexes which are like those obtained by leading from the left ventricular cavity in left branch block, and which consist of a small or medium-sized R wave followed by an S wave of equal or greater voltage. The occurrence of such complexes in leads from the left side of the precordium in left

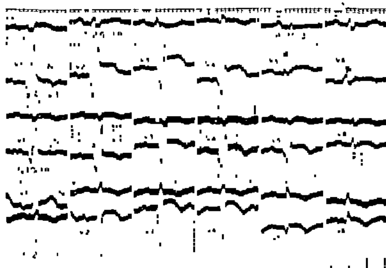


Fig 19 Anterior infarction complicated by transient right bundle branch block (25) First two sets of precordial leads are characteristic of anterior infarction plus right bundle branch block When third set was taken, right bundle branch block was no longer present Patient died on 9-18-38, autopsy disclosed thrombosis of anterior descending coronary artery and a very large anterior infarct Note small initial R waves in leads V_1, V_2, and V_3 of record dated 8-22-38, these apparently represent activation of free wall of right ventricle, which gave rise to the late R waves of previous records

branch block is not reliable evidence of the presence of an infarct We have published observations on one case of left branch block in which these leads showed large QS deflections (26) Autopsy disclosed transeptal infarction plus infarction of the anterior wall of the left ventricle. The combination of infarction of the free wall of the right ventricle and left branch block should theoretically give rise to broad, deep QS deflections in the leads from the right side of the precordium, but such deflections often occur in these leads in left branch block uncomplicated by infarction Modifications of the T complex strongly suggestive of infarction do, of course, sometimes occur when the left branch of the bundle of His is not

functioning They are more likely to be present when the net area of the QRS deflections is small When this area is large its effect upon the character of the T complex tends to obscure them.

Some writers apparently believe that we have overestimated the difficulties of making an electrocardiographic diagnosis of infarction when left branch block is present. What we have said on this subject refers to cases in which this conduction defect is definitely present, and not to cases in

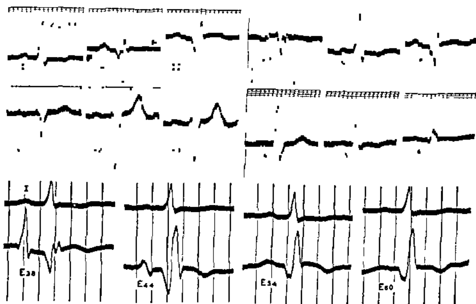


Fig 20 Posterior infarction complicated by arborization block (25) Form of QRS complexes of limb leads is suggestive of posterior infarction plus right bundle branch block, but precordial curves show no evidences of right bundle branch block Leads from ventricular levels of esophagus show broad Q waves followed by very late R waves

which the QRS patterns bear a superficial resemblance to some of those produced by it Other defects in intraventricular conduction are common in myocardial infarction, they do not interfere with the occurrence of abnormally large Q waves or of QS deflections because they do not abolish the initial negativity of the cavity of the left ventricle. Generally, when bundle branch block can be excluded, it is impossible to say whether a lengthened QRS interval is due to a functional depression of the specialized ventricular conducting system or of the ordinary ventricular muscle as a whole, to lesions affecting one or more of the subdivisions of one of the bundle branches, or to involvement of the Purkinje network or subendo-

cardial muscle on the inner aspect of the part of the ventricular wall affected. Oppenheimer and Rothschild (31) gave the name "arborization block," to conduction defects of the last-mentioned type but their criteria for the recognition of this condition have, in our opinion, little or no value. In some cases of infarction, most often when the lesion is an old one, the QRS interval is increased to 0.11 second or more and precordial leads, or leads from the ventricular levels of the esophagus, exhibit a very broad Q wave followed by a tall, very late R wave (Fig. 20) These findings suggest that there is a local defect in conduction which greatly delays the activation

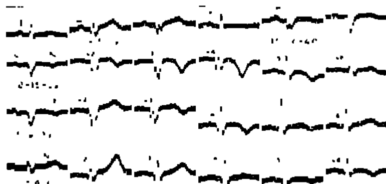


Fig 21 Anteroseptal followed by posterolateral infarction First infarct produced diagnostic changes in QRS and T complexes of leads V_2, V_3, and V_4 and inversion of T wave in lead V_5 Second infarct (last tracing) was followed by appearance of a prominent Q wave and an inverted T wave in previously normal ventricular complex of lead V_6 Note particularly development of R waves in leads V_1, V_2, and V_3 and of large upright T waves in leads V_2 and V_3, and that R waves of these last two leads are preceded by Q waves These R deflections are represented by notches or embryonic R waves in preceding tracing.

of living muscle comprising the outer layers of the involved part of the ventricular wall by slowing the progress of the excitation process through the subjacent part of the Purkinje plexus This is the kind of conduction defect that Oppenheimer and Rothschild had in mind, and it may properly be called arborization block, if it be understood that the criteria advanced by these authors for this diagnosis do not distinguish it from intraventricular block of other types

When, as frequently happens, two or more infarcts differing with respect to age, size, and site, are simultaneously present, the electrocardiographic diagnosis may be considerably more difficult We have seen a number of

instances in which anteroseptal infarction was followed by posterolateral infarction (Fig 21), or vice versa In such cases the second infarct abolishes electric forces originally opposed to the electric forces abolished by the first. Posterolateral infarction following anteroseptal gives rise to the appearance, for the first time, of conspicuous Q waves and terminal inversion of the T wave in lead V_6, abolishes any residual inversion of the T waves in the leads from the right side and central part of the precordium, and often brings about the return of R waves in these leads by changing the level on which any submerged R waves due to the presence of living muscle in the old infarcted area were previously inscribed.

Death from myocardial infarction is so often the result of an unpredictable accident, such as a second coronary occlusion, embolism, the development of ventricular fibrillation, and the like, that it is always hazardous to make any predictions as to the outcome in a given case. Nevertheless, there is every reason for optimism when it is clear that the infarcted region is very small If constitutional symptoms have been absent or trivial, and the electrocardiogram shows (*a*) T wave changes only, (*b*) transient modification of QRS followed by the development of deeply inverted T waves, or (*c*) characteristic changes in both the QRS and the T complex that are confined to one or two precordial leads, there is little reason for concern so far as that particular coronary episode is concerned. An atmosphere of gloom and a too severe or too prolonged restriction of the patient's activities may result in perfect healing of the infarct and the development of a severe anxiety neurosis

Angina Pectoris

Transient changes in the form of the ventricular complex frequently accompany induced or spontaneous anginal pain of short duration We shall restrict our remarks to the changes seen in the limb leads, for precordial leads are not well suited to the study of fleeting disturbances, except when they can be repeatedly induced without danger. The most common phenomena are slight displacement of the RS-T segment, inversion of the T waves, or both; unless these are quite pronounced, it may be difficult to estimate their significance if they have been induced by some means which considerably elevated the heart rate Furthermore, normal subjects who have received digitalis usually exhibit pronounced depression of the RS-T junction and segment after exertion even when there are no conspicuous changes in the T complex, of the kind ordinarily produced by this drug, in the control tracings taken before the exercise test (32).

Occasionally, the changes in the electrocardiogram during an attack of

angina pectoris are comparable in magnitude and similar in kind to those produced by a major coronary occlusion (33). In one of our cases (33) we observed very pronounced upward RS-T displacement in leads II and III accompanied by downward RS-T displacement in lead I, a great increase in the QRS interval, and a change in the shape of the QRS complex. Less marked RS-T displacement of the same kind could be induced by hav-

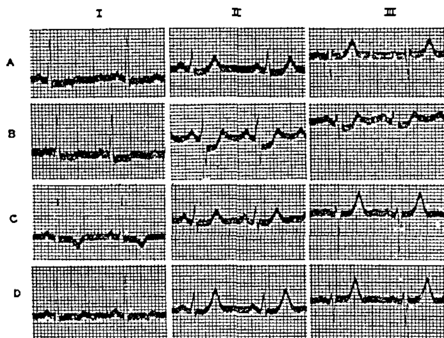


Fig 22 Transient changes in QRS and T complexes during spontaneous attack of angina pectoris (33) A control electrocardiogram B during attack of pain C. five minutes after B, following administration of nitroglycerin (1/100 grain) D. ten minutes after C Note increased size of S and RS-T displacement in leads II and III of B and C.

ing the patient smoke for a few minutes, although this did not elevate the heart rate or the blood pressure and did not give rise to definite anginal pain. In several cases we have observed transient modifications of the ventricular complex of the type illustrated in Figure 22. The tracings reproduced there were obtained before, during, and after a short spontaneous attack of anginal pain They show a transient increase in the size of the S deflection, pronounced transient depression of the RS-T junction and segment in leads II and III, and comparatively little change in the deflections of lead I.

Changes in the T complex of this kind do not occur in any of the more common types of infarction. They suggest the presence of ischemia of the subendocardial muscle of the apical parts of the ventricular walls and may represent effects produced by spasm of the subendocardial arteriolar plexus as a whole.* The opinion seems to be growing that attacks of anginal pain are occasionally, if not frequently, induced by changes in the caliber of altered and abnormally sensitive coronary arterioles in response to influences of various kinds, rather than solely by factors that increase the work of the heart. It should perhaps be mentioned that anyone who for diagnostic purposes makes a practice of inducing attacks of chest pain in cases of suspected angina pectoris must consider the possibility that, sooner, or later, a patient may die during, or very soon after, an induced attack. Having had this experience, we can testify that it is not a pleasant one.

Conditions That May be Mistaken for Coronary Occlusion

Coronary air embolism resulting from the accidental introduction or entrance of air into a pulmonary vein during or after therapeutic collapse of a lung is not extremely rare (34). It may give rise to changes in the electrocardiogram indistinguishable from those produced by coronary occlusion due to other causes. Durant (35) has shown that the injection of a fraction of a cubic millimeter of air into a coronary artery may be fatal in the dog.

We have also observed (36) changes in QRS and in the T complex that were typical of infarction in a case in which the ventricular muscle was invaded by a carcinoma arising in the esophagus. There were abnormally large Q waves, upward RS-T displacement, terminal inversion of T in leads II and III, and very pronounced RS-T displacement in the precordial leads. These changes apparently persisted, with some variation, over a considerable period. It is uncertain whether they were due to a direct effect of the invading cells upon the ventricular muscle or to interference with its blood supply.

Pulmonary embolism is frequently accompanied by right bundle branch block. In such cases, conduction through this branch usually either does not occur at all or is so slow that the electrocardiogram is typical of com-

* Bryant has studied a case in which transient alterations in the QRS and T complexes identical with those shown in Figure 22 were recorded in the limb leads during an attack of severe anginal pain. Precordial leads showed conspicuous upward displacement of the RS-T junction and segment. A day later the patient developed anterior infarction with

plete right branch block, but it gradually improves and becomes normal after several days Whether prominent S waves in lead I and prominent Q waves in lead III, occurring in pulmonary embolism, are always due to this phenomenon or may arise in another way is not yet certain.* There are also transient changes in the level and shape of the RS-T segment. A steplike ascent of this segment has been mentioned frequently in this connection Pulmonary embolism may, perhaps, also produce temporary sharp inversion of the T waves of the leads from the right side of the precordium. It never, so far as we know, produces simultaneous changes in the QRS deflections and the T complex which closely simulate those seen in myocardial infarction. Durant (35) has shown recently that when a considerable quantity of air is introduced into one of the systemic veins of a dog lying on its back or right side an air block of the conus arteriosus results The infundibulum of the right ventricle becomes greatly distended when the chest is open, and unipolar direct leads from its surface display maximal RS-T displacement Death occurs within a few minutes unless the animal is turned on its left side, but this procedure will revive it after it appears to be dead Durant has seen one instance in which an attempt to inject air into the circumadrenal tissues was followed by an accident of this kind. Turning the patient on the left side prevented a fatality.

Various conditions which give rise to severe pain and symptoms of shock may be accompanied by flattening or inversion of the T waves This phenomenon may or may not represent myocardial ischemia, due to the low blood pressure, but to mistake it for evidence of myocardial infarction when, for example, the shock is the result of the perforation of a peptic ulcer would be a serious error It is, however, true that in patients with bad coronary arteries shock, however produced, may give rise to multiple small myocardial infarcts (38)

Pericarditis may produce upward RS-T displacement in leads II and III and in the precordial leads As this displacement declines, sharp inversion of the T waves often develops in the same leads (39) These changes in the T complex are not easily distinguished from those produced by myocardial infarction, although the latter is much more likely to give rise to discordant RS-T displacement in the limb leads than is pericarditis.

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* Further electrocardiographic studies of pulmonary embolism carried out in company with our associates have shown that changes in the QRS complex of the kind referred to here may occur when there is no evidence of complete or incomplete right branch block in the precordial curves It seems probable, therefore, that these changes are often a consequence of rotation of the heart about its long axis due to dilatation of the right ventricle

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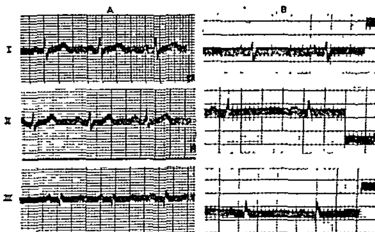


Fig 23 Low voltage deflections in normal electrocardiograms (44) A: 53 year old man who gave no history and exhibited no physical signs suggestive of cardiac disease B 21 year old woman who had always been well and had been active in athletics; physical and roentgenographic examinations of the heart were entirely negative

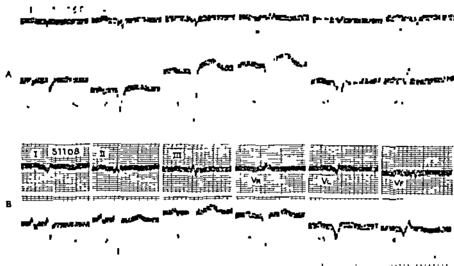


Fig 24 Myocardial infarction in which QRS deflections of limb leads were small and bizarre A. 62 year old man, coronary accident in October 1941, died of cardiac failure on 10-31-44, precordial leads taken 21 days before death strongly suggest old anteroseptal infarction B 47 year old man with symptoms and signs of cardiac failure; no history of anginal pain; precordial curves strongly suggest anterolateral infarction

Pericarditis often complicates infarction and may modify the electrocardiographic phenomena directly due to this lesion. It does not produce abnormally large Q waves or QS deflections, nor does it modify the QRS complex in other ways.

The most regrettable errors in the diagnosis of infarction are those in which the discovery of slight RS-T displacement, basal thickening of the descending limb of R (often mistaken for RS-T displacement), or slight inversion of the T waves in the electrocardiogram of a patient who has recently had pain in the chest, and has not had an electrocardiogram taken previously, leads to the supposition that the electrocardiographic peculiarity and the previous discomfort are necessarily related. Under such circumstances it is no doubt sometimes advisable to restrict the activities of the patient temporarily, but it is imperative that no diagnosis be made until it has been determined by repeating the electrocardiographic examination, several times if necessary, whether the suspicious findings are going to develop into changes that are easier to interpret, or whether they are persistent and have in all probability been present for a long period if not throughout the patient's life Failure to take these precautions is a method of making sick people out of healthy ones.

Slurring, Notching, and Low Voltage

Great care must be exercised in the interpretation of slurring, notching, and low voltage of the QRS deflections, all of which arise in a great variety of ways. There are unquestionably normal persons in whose electrocardiograms the voltage of the largest of the QRS deflections of the limb leads does not exceed 0 2 or 0 3 millivolt (Fig 23) This phenomenon is probably dependent upon a peculiarity in the position of the heart, and this is almost certainly the case if the QRS deflections of the precordial leads are of normal size When there is no other evidence of disease, either electrocardiographic or clinical, low voltage should be disregarded. Low-voltage QRS deflections which are otherwise of normal or relatively normal outline frequently occur in cardiac failure and are relatively common in other disorders that lead to anasarca, pleural effusion, or ascites They are common also in constrictive pericarditis, pericardial effusion, pneumopericardium, and myxedema The cause of the low voltage in pneumopericardium is obviously the insulating layer of air around the heart In conditions associated with an excess of body fluid the low voltage may be due partly or [illegible] rents by the abnor- [illegible] xedema may belong [illegible] hydropericardium

this sort have been described by Wood, Wolferth, and Geckeler (40) and by Öhnell (41) in two cases of anomalous atrioventricular excitation that came to autopsy. However, similar bridges had previously been found in supposedly normal hearts.

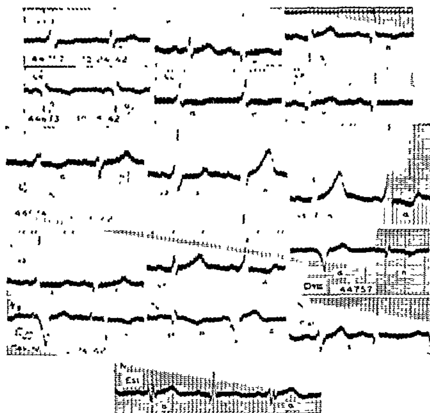


Fig 25 Wolff-Parkinson-White syndrome (42) Normal complexes labeled n, anomalous complexes a Standard limb leads, unipolar limb leads, five precordial leads, unipolar lead from back (mid-line at level of 8th dorsal vertebra), and three unipolar esophageal leads are shown Esophageal leads labeled E followed by a number giving the distance (in centimeters) of exploring electrode from nares

The electrocardiographic evidence seems to indicate that the anomalous atrioventricular bundle is usually on the posterior aspect or on the right margin of the heart, and that the ventricular muscle that is activated prematurely by way of it is on the outer rather than on the inner side of the

The combination of low voltage and QRS complexes of bizarre form in all of the limb leads occurs often in infarction (Fig. 24) and in bundle branch block. In these conditions, the QRS deflections of the precordial leads are usually normal in size, and may be abnormally large, even when those of the limb leads are very small. In such a case it is evident that the QRS complexes of the latter are small and bizarre because the spatial electric axis of the heart is nearly perpendicular to the frontal plane throughout the greater part of the QRS interval. The reason for this probably lies in the position of the heart

Slurring or notching that is confined to leads in which the QRS deflections are small has no important significance. In such leads it results from the combination of potential variations of opposite kinds, derived from two different parts of the heart's surface. In normal precordial tracings, for example, notching of QRS is common in the leads from the transitional zone, and represents the effect of mixing potential variations of the kind that occur at points farther to the left with potential variations of the sort that occur at points farther to the right Slurring or notching that occurs near the isoelectric level is also common in normal curves, and is of doubtful diagnostic value On the other hand, notching that is present in all leads and occurs near the apex of large deflections is probably abnormal. This is the kind of notching that occurs in bundle branch block as the result of incomplete fusion of the septal and mural components of the R wave in leads from parts of the precordium overlying the homolateral ventricle The kind of notching in question may often represent some sort of conduction defect, but too much diagnostic significance should not be attached to it when the QRS interval is well within normal limits.

Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome)

There is a curious anomaly of the heart which is represented by electrocardiograms in which the P-R interval is very short and the QRS interval abnormally long. Many but not all of those who exhibit it are subject to paroxysmal tachycardia As a rule, there are no other signs that the heart is abnormal The administration of atropine, amyl nitrite, or quinidine will sometimes temporarily abolish the electrocardiographic peculiarities In some cases transitions from the anomalous to the normal cardiac mechanism are frequent and occur without apparent cause It is the prevailing opinion at present that this syndrome is due to the transmission of auricular impulses to the ventricles by way of one or more accessory atrioventricular bundles as well as by way of the bundle of His. Extra muscular bridges of

turely. If these are transmitted to the left leg, left axis deviation results; if they are transmitted to the left arm, right axis deviation results. The two groups of cases mentioned cannot be separated by examining the deflections of the limb leads.

Conclusion

We shall not attempt a long discussion of the present wretched state of electrocardiographic diagnosis or the misery attributable to it. The errors made in this field are due in large measure to the same human frailties that are responsible for errors in others, medical and nonmedical. We wish, however, to make a few comments which appear to us worthwhile. In our opinion, no physician should refer a patient to another for an electrocardiographic examination and report without giving the referee a résumé of the data which he has collected (if he has any) nor without letting him know exactly what information the electrocardiographic examination is expected to yield

We think also that there are altogether too many physicians who want to, and try to, read electrocardiograms but are unwilling to go back to the fundamental principles upon which the interpretation of the electrocardiograms must be based In our opinion, it is impossible to use diagnostic criteria intelligently unless they are fundamentally sound and the foundations on which they rest are clearly understood by the user.

There is a wide misapprehension as to the function of statistics in medicine For certain purposes they are of very great value, for others they cannot be more than a temporary and pitiful makeshift When a physician is confronted by a man with bundle branch block, a knowledge of what is wrong with the average man who exhibits this electrocardiographic abnormality is of no great value to the doctor, and is of no interest to the patient. What is to be done depends upon the nature of the underlying disease responsible for the conduction defect If the physician cannot diagnose this disease on the basis of unequivocal evidence, he is not justified in making a diagnosis based on the most frequent cause of bundle branch block or a prognosis based on the average length of life after the discovery of this disorder

Electrocardiography is one of the most exact of diagnostic methods. Its potential value is great, but it is not being used to the best advantage Electrocardiographic abnormalities are not diseases. They have no important bearing upon the life expectancy of the patient, or the extent to which his mode of life should be altered when there is a reasonable doubt as to the nature of the factor or factors responsible for them in that particular case.

ventricular wall. Unipolar leads from the subauricular levels of the esophagus exhibit a broad QS deflection with a heavily slurred descending limb. In the leads from the left side of the precordium, the peak of the R wave occurs at approximately the same time, in relation to the P wave, when the ventricular complex is anomalous as when it is normal. When the normal complex of these leads displays a prominent Q wave, this wave is replaced in the anomalous complex by the premature QRS component which is directed upward and fuses with the ascending limb of R (Fig. 25). This suggests that the cavity of the left ventricle is already positive when the excitation wave which spreads via the bundle of His reaches the ventricles. Although the anomalous QRS complexes of the leads from the left side of the precordium have the same form in all cases, those of leads V_1, V_2 and V_E do not. On the basis of their form, cases of Wolff-Parkinson-White syndrome can be divided into two groups (42). In the first group, the QRS complex of these leads is dominated by a large R deflection which may be broad-topped or bifid, and the premature component is positive and fuses with the ascending limb of this deflection In the second group, the QRS complex is dominated by a downward deflection and the premature component is negative or diphasic. In one case studied by Hecht (42) a change in the location of the auricular pacemaker had a striking effect upon the form of the QRS complexes of the leads from the right side of the precordium, and transitions from the normal to the ectopic auricular rhythm were sometimes accompanied by the occurrence of ventricular complexes of transitional form This suggests that more than one anomalous bundle was present in this particular case, and that the differences between the two groups of cases mentioned may depend upon a difference in the location of the accessory bundle or bundles As might be anticipated, atrioventricular rhythm in which the impulse reaches the ventricles first or reaches the ventricles and auricles simultaneously is accompanied by normal ventricular complexes

In the limb leads the anomalous ventricular complexes are quite variable in form. Left axis deviation is often present when the cardiac mechanism is anomalous in cases in which there is no axis deviation while the cardiac mechanism is normal. On the other hand, the mean electric axis of the anomalous QRS complexes may be deviated to the right or may lie within the normal range These variations are apparently due to variations in the position of the heart, and particularly in the size of the angle made by the long axis of the heart with the frontal plane. The position of the electric axis seems to depend upon the transmission of the potential variations of the posterior ventricular surface, which is activated prema-

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Addendum

Since the foregoing was written, some important contributions have been made to our knowledge of the ventricular complex Leads from the cavity of the human right ventricle (45-47) show that with normal intraventricular conduction the potential of this chamber is briefly positive at the beginning of the QRS interval In left bundle branch block

septum undoubtedly contributes substantially to the initial R deflection in leads from the right side of the precordium and to the Q wave of the leads from the left side (see Fig. 11, page 32)

Other observations (48) indicate that transmural injuries of the ventricular wall produce upward RS-T displacement in leads from the endocardial and from the epicardial surfaces of the injured region. Upward RS-T displacement in epicardial leads, therefore, does not necessarily mean that a layer of subendocardial muscle is less injured than the outer layers Prolongation of systole on the endocardial surface of the ventricular wall produces abnormally tall T waves due to positivity of the epicardial surface (49) The

placement accompanied by terminal elevation of T The last occurs at the height of the reaction, as the RS-T displacement disappears, the T waves become taller, finally assuming their original form when the effect of the original attack or exertion has passed off

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recently reached by Cournand and his co-workers (20,21). Following its use for radiology in Portugal and France, Cournand and Ranges (20) used a long ureteral catheter passed through the arm veins into the right heart, and had the courage to leave it *in situ* sufficiently long to make successive observations By this means they were able to sample mixed venous blood, and could calculate the arteriovenous oxygen difference from simultaneous estimation of the oxygen content of arterial blood McMichael and Sharpey-Schafer (62) have modified the method for clinical use; by avoiding arterial puncture in subjects with normal lungs and making all

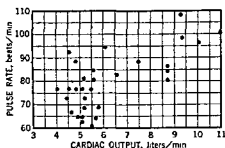


Fig 1 Cardiac output plotted against heart rate in normal resting males in the supine posture, the few with higher output showed faster heart rates (62)

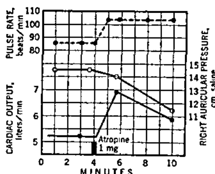


Fig 2 Effect of intravenous administration of atropine on cardiac output (62) Note increase in output followed by a fall as auricular pressure decreases

the gas analyses of oxygen consumption and arteriovenous oxygen difference at room temperature, the calculations have been made as simple as possible This new method has been applied in a very large number of cases and has proved to be entirely safe In the writer's department, experience has run to over 600 cardiac catheterizations without mishap other than occasional local venous thrombosis The latter is usually limited to the elbow region but on two occasions, due to the unwitting use of an acid citrate solution, venous clotting occurred in the axillary veins. In each instance this subsided without more than temporary interference with the patient's welfare By this technic the average resting output of the human heart in a recumbent subject is found to be 5 3 liters per minute with a range of 4 to 8 liters This average agrees well with that obtained by Cournand and his colleagues, who expressed their values as liters per square meter of body surface There is a considerable variation with pulse rate.

Circulatory Failure Studied by Means of Venous Catheterization

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Introduction

The advance of clinical cardiology in the present century has had three distinct phases. The period opens with what may be called the valvular-anatomic outlook, in which the clinical concepts were dominated by simple studies of abnormal sounds in relation to valvular lesions. The second stage was reached with the introduction of Mackenzie's polygraph and Einthoven's string galvanometer, which led to the interpretation of rhythm irregularities and put emphasis on the importance of the heart muscle. This was accompanied by an improved assessment of the individual heart sufferer, based on an estimate of his capacity for effort. At this stage, Mackenzie's teaching dominated British cardiologists and valve lesions took a place of secondary importance. By the end of World War I the abnormalities of rhythm had been fully worked out, and the electrocardiograph passed to a further phase of triumph in the analysis of myocardial disorders. Technical activity directed to electrocardiographic interpretation occupied most of the time of practicing cardiologists, and little emphasis was laid on the study of the main physiologic function of the heart, namely, its pumping action.

In the background, however, receiving only sporadic attention from clinicians, physiologists were actively engaged in efforts to measure the output of the human heart. The way had been shown by Fick (32) in 1870, when he indicated that the output of the heart (in liters/min.) could be estimated by dividing the oxygen consumption in cubic centimeters per minute by the arteriovenous oxygen difference in cubic centimeters per liter. Thus, if one liter of blood passing through the lungs takes up 50 cc. of oxygen, and the oxygen consumption of that individual is 250 cc. per minute, then the cardiac output will be 5 liters per minute. Much effort has been expended in the past in finding the value of the denominator of the Fick equation by complicated respiratory technics. We may by-pass for a moment these complex methods and indicate the solution which has been

not be overlooked in this review. For example, the acetylene method showed that the output of the heart increased by one-third in recumbency over the value obtained in the upright position (56) This has since been confirmed by the catheter method (62). Certain general features found in cardiac failure were emphasized by Harrison (44) ten years ago on the basis of studies with the acetylene method. These observations were extended and confirmed by Altshule (1) and by McMichael (57,58). Among the more important conclusions reached, the following may be cited: (1) the resting output of the failing human heart does not fall much

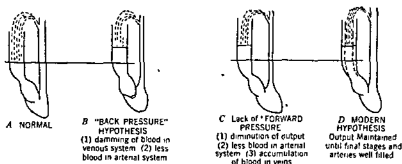


Fig 3 Simplified representation of the various hypotheses of venous congestion (58) B and C Earlier concept, essentially that of passive congestion, since this means more blood in the veins and less in the arteries, the capacity of the "artery" is indicated as smaller D The modern hypothesis, that in the early stages of congestion the output is reasonably well maintained and that venous pressure is raised by blood volume increase or venoconstriction (broken lines) or both

below the normal range until the bedridden state of heart failure is reached, with gross venous congestion, (2) venous pressure may be raised when the patient is at the stage of breathlessness on ordinary activity but still ambulant at this stage the output of the heart is often normal, or nearly so Observations such as these led McMichael (58) to suggest that the rise of venous pressure was not a "back pressure" effect, but rather served as a "compensating mechanism" maintaining the output of the heart at a level as near the optimum as possible until the last stages of heart failure (Fig 3)

Starling's "Law of the Heart." The most fundamental physiologic work for the understanding of the modern outlook on heart disease is that of Starling (78) who from 1914 onward studied the action of the isolated mammalian heart Reference to the original papers and tables is well worth while, as the results are tabulated in detail and Starling's obser-

When the pulse is rapid, output is high (Fig. 1), and this effect is also seen after the injection of atropine (Fig 2). As *pulse rates are more labile in* the young than in the old, the output of the heart is more liable to be fixed at about the average figure (5.3 L./min.) in subjects past middle age.

Table I summarizes *the various methods of estimating cardiac output.*

TABLE I

COMPARISON OF METHODS OF ESTIMATING CARDIAC OUTPUT

Method	Cardiac output, liters/min	
	Range	Average
Direct Fick (the most reliable method)		
Baumann (1930) (cardiac puncture)	.	4.7
Cournand *et al* (1943), McMichael and Sharpey-		
	4-8	5 3
.	5-8	.
	3 7-7 95	
	.	5 8
		6 3
Foreign gas		
Kuhn and Steuber (nitrous oxide) (1910)	3 9-4 7	
Starr and Collins (ethyl iodide) (1931)		4 0
Grollman (1932), Nylin (1931), McMichael (1937) *(acetylene)*		4 0
X-ray		
Eyster and Meek (1920)	.	5 9
Pulse pressure-elasticity		
Broemser and Ranke (1930)	4 2-5 6	.
Injection		
Hamilton, Moore, Kinsman, and Spurling (1932)	3-8 5 (?)*	
Ballistocardiograph		
Starr and Schroeder (1940)		3 3

* Range difficult to determine exactly from data given

Results with Older Methods. The new technic represents the culmination of half a century of striving by a considerable number of physiologists. That their efforts were not in vain deserves our praise and gratitude Those who calculated the output from CO_2 equilibration technics were perhaps the most successful The technic which was most used in the last decade was the acetylene method of Grollman Table I shows that this and other foreign gas methods were subject to a systematic error, making the results too low It is now appreciated that the error arose from the recirculation of acetylene-containing blood during the rebreathing period. The method was thus least reliable when dealing with high outputs.

Although subject to an error (about 20 per cent too low) in normal subjects, it has revealed certain trends in cardiac behavior which should

in the intact man without realizing the necessity of postulating the existence of an important venomotor regulating mechanism. In later pages we shall

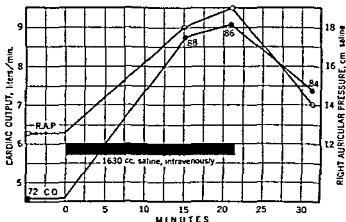


Fig. 5. Effect of raising right auricular pressure by saline infusion; during infusion, cardiac output rises, when infusion is stopped, saline is lost from the circulation and right auricular pressure and cardiac output fall together (62).

see how this concept is used It is worth noting at this stage that Starling was misled about the effects of the heart rate on its output. When he accelerated the isolated heart and maintained a constant inflow, the output did not change, but *he overlooked the significance* of the fact that the output was maintained with a lower filling pressure The data are fully recorded in his tables * Hormonal influences may also alter the capacity of the heart for work, even though the rate and venous pressure remain constant Such an influence is illustrated by the effect of adrenalin. When this substance is infused in very small doses (3 µg /min) *it increases the output of the heart* without significantly affecting the filling pressure, heart rate, or arterial pressure; when the dose of adrenalin is doubled, the rate increases (Fig 7) It is well to keep such influences in

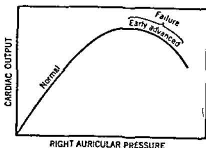


Fig 6 Starling's curve (63) Increase of filling pressure is accompanied by *increase in output until the heart is* overloaded, thereafter output begins to fall

* For example, see Best, C H , and Taylor, N B . Physiological Bases of Medical Practice, 3d ed , p 362 Baltimore, Williams & Wilkins, 1943

vations will always stand as one of the finest basic contributions to the science of cardiology. Starling showed that the main factor determining the output of the heart was venous filling pressure. The filling pressure determines the diastolic length of the myocardial fibers, which in turn determines the strength of the subsequent systolic contraction. The effect of alterations of the filling pressure in the human heart are shown in Figures 4 and 5. When the auricular pressure is raised, the output increases, and conversely, lowering the right auricular pressure reduces the output.* As the heart lies well above the body's center of gravity, the venous return is impaired by pooling of blood in the lower part of the body when in the upright position The increased output when the body is recumbent is the result of increased pressure in the neighborhood of the right auricle In Starling's work, however, it was shown that the increase in output with a rising filling pressure took place only through a certain range. If the pressure is increased beyond a certain value the output will flatten out, and if the pressure is further raised the output will begin to fall. These relationships are seen in Figure 6.

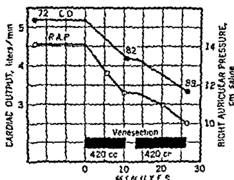


Fig 4. Effect of venesection on cardiac output and right auricular pressure In this and Figures 5 and 7, numbers on cardiac output line indicate heart rate Right auricular pressure is measured in supine position anterior to the posterior surface of the back (62).

In addition to the action of the filling pressure, changes in the output of the heart result from certain other influences which must be defined at this stage A rapid heart rate will increase the output if the venous filling pressure remains constant. This is shown by the injection of atropine, which increases the output of the heart considerably at first; a minute or two later the venous pressure falls and the output settles again toward its original level (Fig 2, page 65). The nature of this venous pressure adjustment is not known, but it is impossible to do much work on the heart

et al

Such adaptive mechanisms as adrenalin secretion and hypertrophy may come into play. Sooner or later, in most cases of long-continued overloading, whether by hypertension or valvular defects, a point is reached at which the output of the heart will tend to fall, although this tendency may be counteracted for a time by further rises in venous pressure.

At the stage of the first rise in venous pressure the cardiac reserve, i e., the heart's capacity to increase output, diminishes considerably (57,58). It is the inability to increase cardiac output without a gross increase in filling pressure which brings about congestion of the lungs and dyspnea. Sooner or later, too, systemic venous congestion is accompanied by edema.

The rise in venous pressure, which at first may be beneficial in some respects, in the later phases seems to carry the heart "over the top" of the Starling curve; any further rise of pressure is accompanied by dilatation of the heart beyond the optimum and a further fall in output. At this stage, *the patient is usually breathless at rest, with a very considerable* rise of venous pressure The output is now well down and figures of 3 liters per minute are common The output, however, seldom falls below 2 5 liters per minute until death is imminent

The Action of Digitalis. Although digitalis has been in use for a century and a half, its mode of action has been but poorly understood Following Mackenzie's demonstration of its action in reducing ventricular rate in auricular fibrillation, his school, developed by Lewis, led a considerable body of opinion in Great Britain to believe that digitalis only acted beneficially in heart failure with fibrillation This view, however, was opposed by many clinicians, for example, Christian (13), Luten (55), Gavey and Parkinson (38) Most pharmacologists thought that the drug acted by having a direct stimulating effect on the myocardium, but others were unconvinced by the experimental work (48) In 1925, Harrison and Leonard (45) showed that digitalis lowered the venous pressure as well as the cardiac output of normal dogs The venous pressure action was confirmed for normal man by Rytand (71) and for patients in heart failure by Stewart *et al.* (82) and by Wood (89) This lowering of venous pressure appears to be the most constant effect of digitalis Its mechanism in animals has been studied by Dock and Tainter (24) and by Katz *et al* (49) These workers believe that the portal pressure rises as the systemic venous pressure falls, and that the mode of action is a venoconstrictive effect in the liver That digitalis has no constricting effect on the *hepatic* veins of man is quite certain, since Wood showed that the liver in congestive failure shrank itwh the venous pressure fall induced by digitalis

While the action of digitalis on the normal heart is to reduce the output,

mind, as sometimes changes are seen in the output of the heart which are not explicable in terms of altered rate or filling pressure (84a)

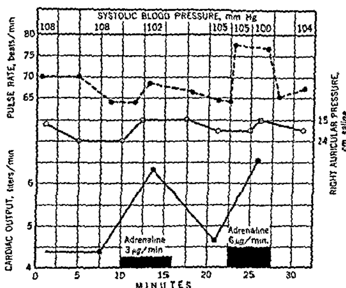


Fig 7 Effect of adrenalin infusion (62) Note increase in cardiac output with the smaller dosage, without significant change in heart rate, arterial pressure, or right auricular pressure

Heart Failure

Heart Failure with Low Output

The normal heart can always meet a demand for increased work by an increase in filling pressure When the heart is subjected to an increased load, for example in acute hypertension, the result is an increase in the venous pressure, first in the pulmonary veins and later in the systemic veins These consequences of acute hypertension were seen in Starling's experiments on the isolated heart when he produced an acute rise of arterial resistance, it raised the pressure in all chambers of the heart, including the right auricle In acute nephritis the rapid rise of arterial pressure is probably always accompanied by a rise in venous pressure and a concomitant increase in cardiac size (52)

When the overload becomes chronic, as in most cases of essential hypertension *and in many instances of* "compensated" valvular disease, the heart maintains the increased work without any measurable rise in venous pressure. We do not yet know what the influences are which determine this capacity for increased work in the absence of a rise in venous pressure

that the rise in output of the failing heart might mean that digitalis did indeed have a direct stimulating effect on the cardiac muscle, an action long suspected by clinicians and laboratory workers. In order to get evidence on this point, McMichael and Sharpey-Schafer lowered the venous filling pressure by means of congesting cuffs round the thighs, so that the subject

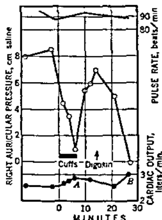


Fig 9 Hypertensive failure with sinus rhythm (63) A: Lowering of right auricular pressure by congesting cuffs on the thighs produces a small but significant increase in cardiac output B After release of cuffs, 1 5 mg digoxin produces a similar increase in cardiac output

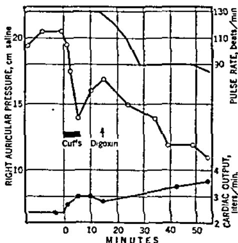


Fig 10 Mitral stenosis and hypertension, with auricular fibrillation and congestion (63). Mechanical lowering of right auricular pressure without rate control increases cardiac output Digoxin subsequently produces proportionately greater effects both on cardiac output and right auricular pressure Fall in heart rate has little effect.

is "bled" into his own legs and the pressure in the great veins round the heart can be lowered by several centimeters, as measured by a saline manometer It was found that this mechanically induced fall in venous pressure produced a rise in cardiac output of a degree exactly similar to that produced subsequently when the venous pressure was reduced to the same level by digitalis (Figs. 9 and 10). When a mechanically produced fall in venous pressure had no effect, digitalis also produced no measurable effect on that particular heart It seems, therefore, that the effect of digitalis on cardiac output is mainly the result of a primary action on the venous pressure.

Attempting to analyze the meaning of these observations, we are thrust back to a consideration of Starling's curve which, as already anticipated,

the action in patients with heart failure is much less certain Stewart and his colleagues (82) thought that an increase in output was measurable in every case, while Harrison (44) could not confirm this He got very variable effects, and was very critical of the work of Stewart's school.

Applying the new method of venous catheterization, and with a standard dose of 1.5 mg. of digoxin intravenously in all cases, McMichael and Sharpey-Schafer (63) found that, at first sight, the output of the heart behaved in a rather erratic fashion. Nonetheless, all cases showed a fall in venous pressure and could be separated into three main categories: *(1)* those with a fall in output were either normal subjects (Fig. 8) or had

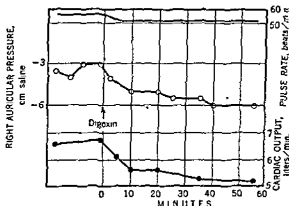


Fig 8 Effect of 1 5 mg digoxin on normal subject In this and subsequent figures *right auricular pressure is measured in centimeters saline above or below the sternal* angle (normal, −5 cm) (63) Note parallel falls in cardiac output and right auricular pressure

an initially high cardiac output for some reason, e.g , anemia; *(2)* those with rising output after digitalis, who were all in severe congestive failure with an initially low output, *(3)* those in whom the output of the heart showed no significant change with digitalis These last were either in early failure or had reached a late irresponsive phase of the disease

It was at first difficult to understand why, with a falling venous pressure, the output of the heart behaved in such a variable fashion. *The fall in venous pressure clearly could not be fully explained by the increasing heart output, as it could also occur unaccompanied by a change or even with a fall in output* Looked at from this last angle, it seemed probable that digitalis had a primary action on venous pressure and that the fall in venous filling pressure might be the cause of the fall in output of the normal heart, a suggestion already made by Dock (21). In this case it seemed possible

that the rise in output of the failing heart might mean that digitalis did indeed have a direct stimulating effect on the cardiac muscle, an action long suspected by clinicians and laboratory workers. In order to get evidence on this point, McMichael and Sharpey-Schafer lowered the venous filling pressure by means of congesting cuffs round the thighs, so that the subject

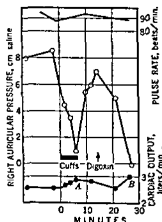


Fig 9. Hypertensive failure with sinus rhythm (63) A: Lowering of right auricular pressure by congesting cuffs on the thighs produces a small but significant increase in cardiac output B After release of cuffs, 1 5 mg digoxin produces a similar increase in cardiac output

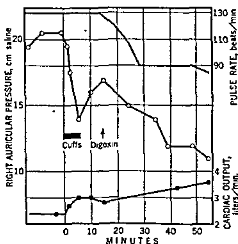


Fig 10 Mitral stenosis and hypertension, with auricular fibrillation and congestion (63) Mechanical lowering of right auricular pressure without rate control increases cardiac output Digoxin subsequently produces proportionately greater effects both on cardiac output and right auricular pressure Fall in heart rate has little effect

is "bled" into his own legs and the pressure in the great veins round the heart can be lowered by several centimeters, as measured by a saline manometer. It was found that this mechanically induced fall in venous pressure produced a rise in cardiac output of a degree exactly similar to that produced subsequently when the venous pressure was reduced to the same level by digitalis (Figs 9 and 10) When a mechanically produced fall in venous pressure had no effect, digitalis also produced no measurable effect on that particular heart It seems, therefore, that the effect of digitalis on cardiac output is mainly the result of a primary action on the venous pressure.

Attempting to analyze the meaning of these observations, we are thrust back to a consideration of Starling's curve which, as already anticipated,

provides a possible answer to our problem. If the failing heart is behaving like an overloaded heart beyond the summit of Starling's curve, then a reduction of venous filling pressure will lead to an improvement of output. This concept also fits in with the observed reduction of heart size after digitalis, so carefully measured by Stewart and his co-workers.

Effects of Venesection. To obtain completely comparable results from digitalis and from a mechanical lowering of venous pressure, venesection and retransfusion would be desirable, but this is not a safe procedure with the cardiac invalid, since transfusion may precipitate severe failure. However, venesection alone has produced drops in venous pressure with accompanying rises in cardiac output as good as the most favorable results from digitalis (Fig 11).

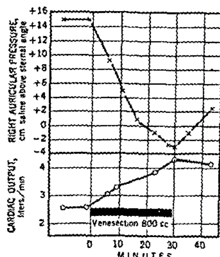


Fig 11 Hypertensive cardiac failure Venesection with removal of 800 cc of blood lowered venous pressure and increased cardiac output from 2 6 to 4 3 liters per minute (46a)

The best test of the effects of venous pressure reduction on the failing heart is provided by cuffs on the thighs, as these may raise the heart output without any accompanying change in arterial pressure Large venesections are accompanied by a fall in the arterial pressure, while large doses of digitalis leave the arterial pressure unchanged, or even slightly raised This makes difficult a detailed comparison between the two, as the heart does more work after digitalis than after venesection This is the only evidence from catheter experiments which might be considered as supporting the theory of a direct stimulating action by digitalis on the failing heart So far, however, the cuff experiments strongly support the opinion that reduction in venous pressure is mainly responsible for the improved cardiac output after digoxin

Rate Control The effect of controlling the heart rate in auricular fibrillation has still to be worked out completely From the observations of McMichael and Sharpey-Schafer (63), rate reduction had little measurable effect (see Fig 10) In the data collected by them, the increase in output achieved by digitalis *in fibrillation was no greater than that seen* in cases with sinus or normal rhythm, where rate change was only slight

After initial digitalis control in fibrillation, atropine may set the rate back to a high level without reduction of output, sometimes in fact further increasing output. Detailed analysis and prolonged follow-up are needed to settle the problem of whether rate control has any beneficial long-term influence. In the meantime, we may say that rate control is of secondary importance and that the mechanism reducing venous pressure plays the major part in causing improvement of heart output in the cardiac invalid.

Animal Experimentation with Digitalis. If the view of digitalis action described above proves to be correct, doubt will be cast on much of the pharmacologic work of the past two generations. It may be interesting to consider briefly how some of the generally held opinions have arisen

Withering introduced digitalis as a diuretic for the treatment of dropsy, and though he noted its value in cases where the pulse was feeble or intermittent, little was done to put its mode of action on the heart on a sound scientific basis until it was systematically studied by Sir James Mackenzie. We have already noted how he and Lewis led a school of thought ascribing its benefits mainly to rate control in auricular fibrillation Occasional striking clinical responses without rate control compelled direct pharmacologic studies on the isolated mammalian or frog heart. Cushny (22) thought that the action on the diseased ("malnourished") human heart was more likely to resemble the action on the frog heart and he devotes much of his detailed description to work on the frog heart. Usually far too large doses of digitalis were used and; apart from an initial slight increase in excursions of the lever, the records often show a steady decrease in amplitude of contractions as the heart becomes poisoned by the drug (23)

Cohn (15) stated that "if digitalis increases the ability of the ventricles to pump blood, it does so by means of a change which is more subtle than can be distinguished by our methods" Cohn and Levy (16) used a myocardiographic lever and by this means thought that *sometimes* the contractions of the heart increased in normal dogs and cats But since they were measuring only *linear* contractions of the heart muscle, it is obvious that the changes they observed could be accounted for by a reduction in venous pressure and cardiac *size*, and that no conclusions on output could really be drawn from such experiments. With reduction in cardiac size a greater linear contraction is necessary to maintain the same stroke output.

The attitude of Lewis twenty years ago in clinging to the demonstrable effects of the drug in controlling rate in auricular fibrillation is not surprising, in view of this doubt and perplexity regarding the mode of action of digitalis in heart disease The pharmacologic search for another explana-

tion still continued and it was hoped that the heart–lung preparation might yield an answer. Gremels (41) found no change in the output of the camphor-poisoned heart when strophanthin was given, but the heart did the same amount of work with a lower oxygen consumption. This type of experiment was severely criticized by Katz and his co-workers (48).

Failure to control all the variables is responsible for some of the errors that have crept in. *Conclusions as to the mechanical efficiency of the heart* are especially prone to such errors, because of variations in the oxygen uptake by the lungs Katz and co-workers (48) used a *single circuit isolated* heart preparation, in which living tissue other than the heart was excluded; in this experiment they could find no beneficial effects from digitalis either on work or mechanical efficiency. Interesting and important results were, however, obtained by Cohn and Steele (17) when the heart–lung preparation in "spontaneous" failure was digitalized They say, "The pressure in the right auricle, having risen, fell; the heart, having dilated, contracted, and the output, having fallen, rose." Later, in the clinical section of the same series of outstanding papers, Stewart and Cohn (81) concluded that the output of the normal heart goes down, while that of the failing heart increases. Digitalis was thought to decrease cardiac size and this made the *normal heart too small, while it restored the diseased heart to a more suitable volume*

These conclusions come very close to our own, both sets of observations having left an obvious gap in information, namely the changes in pulmonary venous pressure It is quite possible that digitalis may diminish the tone of this part of the venous system, and that it is here that relief of left ventricular overloading may take place Further work from the clinical angle is obviously required in cases of heart failure with predominant left ventricular failure and pulmonary engorgement, and the response of lung vessels to digitalis in the heart–lung preparation would repay further study.

One other important type of experimental measurement needs comment Wiggers and Stimson (88) noted that with digitalis there was an increased gradient of pressure development in the ventricle and that a higher pressure maximum was reached. However, since the ventricle was found to be dilated with digitalis, this might account for many of the changes recorded. This dilatation with digitalis indicates that the experimental conditions were too abnormal to be of value in explaining the drug's action in man, where its effect is to reduce cardiac size, both in *health and in disease* (81). Cattell and Gold (12) found that digitalis increases the tension achieved

in isolated strips of cat's papillary muscle. Here again the conditions are very abnormal.*

These inconsistent observations could be expanded by further references to the literature, but perhaps they are easily understood when we realize that there is now unanimity of opinion that digitalis reduces the output of the normal heart (24,45,63,81). As most animal experiments were conducted with "normal" hearts, it is difficult to see how an improvement in output could be demonstrated Some hearts, however, were deteriorating, and it is possible that in these some slight stimulating action could be recorded.

Cohn (15) says: "The methods employed in pharmacology are not superior to those now available in clinical medicine." This remark, as true as it was in 1915, is even more true today when we can make accurate observations and measurements on nearly all the essential physiologic factors of cardiac behavior in clinical cases. We therefore feel justified in the following conclusion: *Direct study of the isolated heart has failed to demonstrate any consistent direct action of digitalis in increasing the strength of myocardial contractions It is possible that such an action exists in the failing heart,** but it is of minor importance in clinical therapeutics compared with the action of digitalis in reducing venous pressure The exact mechanism of this peripheral action still remains to be determined*

Cushny (23) stated. "In hearts which present no anomalies of rhythm . . . the effects of digitalis are still a matter of question " And he went on

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* [illegible]

** [illegible] the editors believe the myocardial action to

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Figure 12. This increased circulation is probably maintained by two mechanisms: first, by an increased heart rate, and second, by a rise of venous pressure. It is interesting that the rise of venous pressure in such cases occurs without any increase of blood volume (61,74). This is an important point, as in ordinary congestive failure with low output blood volume is increased and there is a significant correlation between this increase and the height of the venous pressure. In these cases of "anemic heart failure" the rise in venous pressure cannot be ascribed to failure of

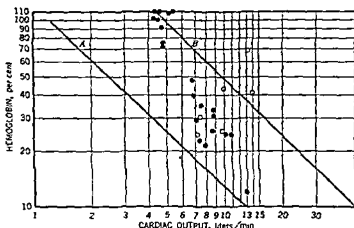


Fig 12 Cardiac output plotted vs hemoglobin concentration on a logarithmic scale (74) A, 100 per cent utilization of available oxygen at an oxygen consumption of 250 cc. per minute (minimum possible cardiac output at different hemoglobin levels), B, 25 per cent utilization of available oxygen. The 9 circles at the top of line B, data from normal subjects over age of 40, remaining black circles, data from anemia patients; open circles, posthemorrhagic cases (Courtesy of Dr Sharpey-Schafer)

the heart to keep on pumping blood through the body at an adequate rate, as the output is usually more than double the normal value. The pulse pressure is increased, indicating that the arterioles are dilated (the output being high and the mean arterial pressure somewhat reduced). Since the volume of blood in circulation (often below 3 liters) must be equal to the capacity of the total vascular bed, the latter must be markedly reduced. This reduction does not take place on the arterial side; as the larger veins are full and often distended, it must take place in the capillaries and venules It is on such clinical evidence that we find it necessary to postulate an active venomotor mechanism for maintaining and even raising the venous pressure to the required level

to say: "There is no doubt of the benefit attending the use of digitalis in some of these cases, while there is as little question that in others the treatment is valueless; and at present it is not possible to differentiate between these." In the next section a group of cases will be described in which digitalis administration seems to be useless.

Heart Failure with High Output

In certain circumstances the output of the heart has to be increased to meet the need for a better oxygen supply, or to overcome certain, anatomically produced, mechanical difficulties in the circulation. The conditions demanding such an increased cardiac output may be listed as follows: (*1*) severe anemia; (*2*) emphysema heart (cor pulmonale); (*3*) thyrotoxicosis; (*4*) beriberi; (*5*) free arteriovenous "communications," to which group belong (*a*) traumatic arteriovenous aneurysms, (*b*) generalized osteitis deformans, (*c*) congenital faults, including patent ductus arteriosus and patent interauricular septum, and (*d*) placenta in pregnancy.

In the first two conditions the oxygen content of the arterial blood is much reduced, and an increased circulation rate partially overcomes the problem of maintenance of a suitable "pressure head" of oxygen in the capillaries In thyrotoxicosis, the output of the heart is increased parallel with the metabolism and the increased heart rate. Beriberi is sometimes associated with a high pulse pressure and probably a rapid circulation rate, but the writer cannot speak from any direct experience with this disease.

All these conditions have certain features in common. the hands are warm; the peripheral pulses are full and bounding, pulse pressure is high. In spite of these features, the patients are often breathless and venous congestion and edema may be present In the thyrotoxic group, however, stages are reached where the output, initially high, becomes lower than normal

Anemia. Owing to the lowered oxygen content of the circulating blood, proper oxygenation of the tissues is impossible unless the cardiac output is increased. Every clinician has encountered a low hemoglobin compatible with the maintenance of life, usually about 10 to 12 per cent of normal value, and thus representing an oxygen carrying capacity of 20 cc. per liter of blood instead of the normal 200 cc To maintain an oxygen consumption at rest of 240 cc. per minute, even full utilization of all the oxygen in such blood, assuming full saturation, would require a cardiac output of 12 liters per minute (i e , 240 − 20). At such hemoglobin levels, the cardiac output has been found to be only slightly above that minimum figure (74). The increased output in anemias of various grades of severity is shown in

When digitalis is given these subjects it may lower the venous pressure and with it the cardiac output. Digitalis, therefore, is valueless as a method of treatment except where it is used to control the venous pressure level during transfusion

A special group of cases of heart failure with high output is exemplified by conditions with free arteriovenous communications. An excellent example may be found in generalized Paget's disease of bone (29) In the

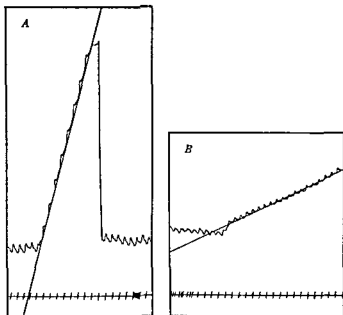


Fig 14 Blood flow through a leg with Paget's disease of tibia (A) compared with opposite normal limb (B), each measured by a plethysmograph using the same volume recorder (29) The steeper the slope, the greater the blood flow In diseased leg flow is 4 5 times as great as in normal leg

latter state, the blood flow through the affected bones is greatly increased, due to the great vascularity of these bones. When the disease becomes generalized, the flow through the affected bones may amount to as much as 3 to 4 liters per minute (Fig 14), and at this stage heart failure appears with a very high cardiac output (Fig 15) In the case recorded by Edholm and his co-workers (29), the output of the heart was over 13 liters per minute Further unpublished studies on such cases show that they may not be at the critical part of Starling's curve. Administration of atropine and

That the muscular walls of veins are subject to venomotor regulation now seems to be well established. Gollwitzer-Meier and Bohn (40) showed that increase in the carbon dioxide content of the blood produced venoconstriction through the mediation of sympathetic nerves. Fleisch (34) showed that the caliber of veins was reflexly influenced from the carotid sinus. Donegan (25) and Beckmann (4) have also demonstrated that the veins contract in response to asphyxia and acidosis. Beckmann's results show that the veins are very sensitive to small changes in hydrogen ion concentration well within the limits of the physiologic range.

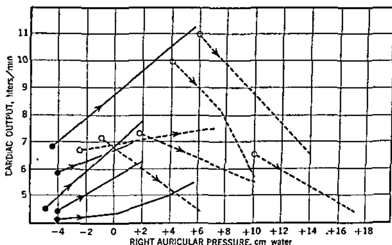


Fig 13 Effects of raising venous pressure by transfusion Comparison of response of anemic (- - -) and normal (—) hearts to raised filling pressure, output of anemic heart may fail to rise or may fall, indicating that it lies on or beyond the summit of Starling's curve (74a)

These mechanisms, however, may not account entirely for the venous pressure change in anemia with low blood volume The high cardiac output with raised venous pressure does not develop until perhaps 24 hours have elapsed after a severe gastrointestinal hemorrhage. Some slowly acting chemical or hormonal mechanism may be responsible

The behavior of the heart in anemic failure shows that when the venous pressure is increased still further, e g , by transfusion, the output falls, as can be seen in Figure 13 (74a) It is thus likely that the anemic heart, pumping 7 to 11 liters per minute, lies at the top of its own Starling's curve, where a further increase of venous pressure will push the output down and render the state of that particular patient very precarious All clinicians have seen fatal pulmonary edema result from transfusion in severe anemias.

about 3 to 4 liters, leaving a blood flow through the rest of the body of at least 9 liters per minute. This seems to dispose finally of the often held hypothesis that anoxia of the capillaries plays a part in the production of cardiac edema.

Cor Pulmonale. McMichael and Sharpey-Schafer (63) called attention to the fact that cases of cor pulmonale may have a high cardiac output. These were patients with emphysema and gross venous congestion, in whom the arterial oxygen saturation was very low. We have encountered with considerable frequency arterial oxygen saturations of about 70 per cent, and have seen one as low as 35 per cent saturation. As regards oxygen supply to the tissues, patients in this condition are in a plight *somewhat similar to the anemic patients* Whatever the mechanisms subserving the increase in cardiac output in severe anemia, they seem to come into action also in patients with severe pulmonary anoxia as exemplified by emphysema The cardiac output figures in such patients are less high than in anemia, ranging from 6 to 10 liters per minute. Similar figures have been obtained by Richards (68a) These patients usually fall on the "normal" side of Starling's curve, as lowering of the venous pressure by venesection or digitalis leads to a fall in cardiac output. It has long been known that patients with severe cor pulmonale from emphysema are most difficult to treat, and one recollects cases in which death seems to have followed rapidly on attempts at digitalization,

The demonstration of an increased cardiac output in cases of emphysema heart may have some bearing on the somewhat mysterious nature of its development. As the capacity of the pulmonary vessels has been calculated to be nearly one liter (87), an immense proportion of these must be destroyed before an effective resistance to pulmonary blood flow is created. It is noteworthy that in the late stages of cor pulmonale edema of the lung bases is common, a phenomenon difficult to explain except on the basis of a failing left heart as well The extra demand on the whole heart in such patients seems now to be apparent

Thyrotoxic Heart Failure. It might be thought convenient to include this group under the heading of cardiac failure with high output Many authors have claimed that the cardiac output in hyperthyroidism is raised out of proportion to the metabolic rate (7,37) In a limited number of observations, however, we have found that the arteriovenous oxygen difference is often within the normal range and the cardiac output increased in proportion to the metabolic rate Output is sometimes raised out of proportion to the metabolic rate and part of this increase may be accounted for by the rapid heart rate. Further, when thyrotoxic patients go into cardiac

raising venous pressure by saline infusion may increase the heart output, but if pressure is raised sufficiently high an attack of dyspnea or orthopnea may be precipitated on a rising output curve (unpublished observations) Eppinger, von Papp, and Schwarz (30) thought that orthopnea might occur with a rising cardiac output, an observation frequently scorned in subsequent

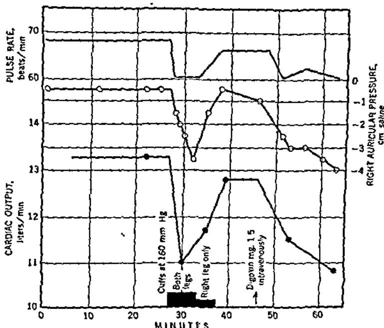


Fig 15 Cardiovascular reactions in generalized Paget's disease, when circulation through legs is shut off by cuffs (29) Pulse rate, venous pressure, and cardiac output fell, similar to reactions accompanying partial closure of traumatic arteriovenous aneurysms, digitalis produced parallel falls in venous pressure and cardiac output

writings on heart failure There can be no doubt, however, that orthopnea can be precipitated by the high pulmonary vascular pressure which accompanies a rising output

In these cases of cardiac failure with free arteriovenous communications, edema may be a pronounced feature even at the stage at which considerable further increases in output are still possible and at which the patient complains of little dyspnea In addition to the high rate of circulation through the shunt in the bones, there is evidence that the circulation through the other tissues of the body is increased as well. Thus, in the case described by Edholm *et al* (29), the bone blood flow was estimated at

ative intrathoracic pressure of about 5 centimeters of water, or a total of 8.5 centimeters of water. This differential pressure is subject to considerable variation on either side of the mean value Fletcher's observation upholds the view of most physiologists, e g., Katz (47), that the hydrostatic pressure in the right auricle determines the output of the heart only insofar as it regulates the length of the myocardial muscle fibers

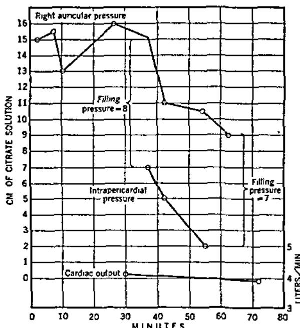


Fig 16 Malignant pericarditis Filling pressure of heart (right auricular minus pericardial pressure) remained the same during withdrawal of 100 cc of pericardial fluid (from 38 to 56 minutes), cardiac output and filling pressure remained essentially unaltered (Courtesy of Dr C M. Fletcher)

Presumably, when the pericardial pressure gets to such a high level that it begins to approach the venous pressure, the output of the heart will begin to fall Soon afterward, as in classic "shock," the arterial blood pressure will begin to fall also, and ultimately death will follow

Concretio Cordis. So far little has been done on this subject with the new method Since the rigid case around the heart prevents expansion, the diastolic fiber length remains unaltered and the stroke output may therefore be expected to be constant. This is suggested by the figures ob-

failure, our experience indicates that the cardiac output may be low. In one such case a most satisfactory cardiac response to digitalis was obtained (63, Case 17). Further work is required with the new method on this important group.

Pregnancy. The placenta may well constitute an arteriovenous shunt. Stander and Cadden (76), using the acetylene method, found that the cardiac output rose during pregnancy from the fourth month onward At term it may be 50 per cent above the normal average. This, together with the increase in blood volume and hemodilution, resembles in many ways the state of affairs noted in arteriovenous aneurysms and in Paget's disease (29) These added strains may precipitate the signs of heart failure in patients who in a nonpregnant state would have shown little sign of cardiac distress. In view of our findings regarding the special difficulties in the therapeutic use of digitalis in "high output" failure, a study of the circulation during pregnancy by the catheter method is clearly desirable.

Pericardial Disease

Pericarditis and Effusion. How pericarditis with effusion affects the circulation has been a subject of much experiment and speculation From experiments with oil injections into the pericardium, Cohnheim (18) and Starling (77) visualized a sequence of events as follows: As the intrapericardial pressure rises, a rise in venous pressure parallels it until a critical point is reached, at which the arterial pressure begins to fall The venous pressure rise was thought to be caused by the damming back of blood in the veins, diminished inflow to the heart resulting in a fall in the cardiac output, compensated at first by vasoconstriction, when the output falls still further, the blood pressure begins to drop and death ultimately ensues.

That this idea is not universally applicable has been shown by the work of Fletcher (35) in this school In a case of malignant pericarditis he showed that the difference between the intra-auricular and the extracardiac pressure was 8 centimeters, and that this difference in pressure remained the same when the venous pressure was reduced following withdrawal of 100 cc. of fluid from the pericardium Cardiac output remained unchanged at approximately 4 liters per minute while the fluid was being taken off. These findings are shown in Figure 16. It is clear that the rise in venous pressure compensates for the rise in extracardiac pressure and keeps the effective filling pressure constant Richards and his collaborators (69) have shown that the normal average effective filling pressure of the right auricle is the hydrostatic pressure of 3 5 centimeters, plus the neg-

carditis. The bronchiolitis was interfering considerably with oxygenation of the arterial blood which was 79 per cent saturated in the single sample taken, and such values are certainly liable to fluctuation. Hence the apparent differences in cardiac output determinations and the necessity to draw a line through somewhat scattered points in the diagram.

Burwell and Strayhorn explain the close interdependence of cardiac output and cardiac rate in their case of constrictive pericarditis with low output as due to: "limitation of the diastolic relaxation of the heart by the encircling scar tissue and the consequent fixation of the output per beat at an abnormally low level. This limitation of the output per beat made it impossible for the output of the heart per minute to increase except so far as this could be brought about by increase in the already rapid cardiac rate."

With this conclusion and interpretation we are in entire agreement. Burwell and Strayhorn noted that digitalis lowered the output in their case, apparently by diminution of rate (sinus rhythm). We can add the further conclusion that even in the presence of auricular fibrillation with a rapid ventricular rate, digitalis control of rate will also lower the output. The output may be subsequently increased if the rate is set back to, or above, the original level with atropine It is of course impossible to speak of constancy of stroke output in the presence of fibrillation, but the *average* stroke output must remain essentially unchanged for the reasons as given above by Burwell. Further, the cardiac output seems to depend on rate alone, irrespective of considerable changes in the hydrostatic filling pressure, so long as this pressure is sufficiently high to fill the chambers of the heart completely during diastole Thus the rate effects differ from those observed with atropine on a healthy heart (see Fig 5).

Congenital Heart Disease. The cardiac catheter has a distinct place in the study of developmental abnormalities of the heart In the cyanotic group, the arteriovenous oxygen difference can be found by simultaneous arterial and right heart samples An estimate of the volume of blood shunted through the septal defect may also be made on the assumption that the arterial blood is a mixture of right heart blood and blood which has been 95 per cent saturated with oxygen in passage through the lungs. So far there are no records of the use of the cardiac catheter for this purpose.

In the acyanotic group, the catheter may be used to detect a left-to-right shunt by a gross difference between the venous blood in the great veins and that in the right auricle or ventricle which has received a gross admixture of arterial blood from the left side of the heart. Examples of this

tained by Burwell and Strayhorn (11), using the acetylene technic, whose data are plotted in Figure 17.

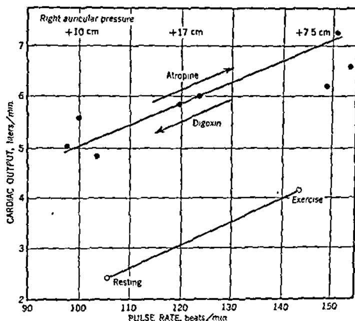


Fig 17 Cardiac output in concretio cordis (35) Open circles data of Burwell and Strayhorn, dots author's data Diastolic size of heart is fixed and stroke output therefore predetermined Change in minute output is parallel to rate, irrespective of filling pressure.

The writer's personal observations are limited to one patient, who died of complicating bronchiolitis·

A woman aged 64, suffering from chronic bronchitis, was admitted to the hospital in severe heart failure The veins were engorged, there was gross edema, and cyanosis was deep. X-ray showed a rim of calcium along the left border of the heart Auricular fibrillation was present, with a ventricular rate of 124 per minute The cardiac output averaged 5 9 liters per minute. Digoxin, 1 5 mg, reduced the ventric- ... cardiac output to an average of 5 liters per

minute.

... satisfactory, as the patient was suffering

heart failure the output cannot increase at all The limitation of cardiac reserve is therefore the essential feature of the failing heart in the early stages, while in the later phases of cardiac failure the maintenance of a normal cardiac output is only achieved by a considerable rise in venous pressure. In the final stage, the venous pressure goes on rising to a level at which it is actually harmful. How this stage is reached we do not yet understand. It may be that physiologic mechanisms go on raising the venous pressure in response to an anoxic stimulus, or alternatively, that the venous pressure is raised by the patient's efforts to take exercise. Schott (73) and Tetelbaum and his associates (83) showed that the rise in venous pressure after exercise was greater and more prolonged in cardiac patients than in normal subjects.

That pulmonary congestion may cause dyspnea has long been suggested by numerous investigators (14) Our work fully supports this view; in one instance we have actually seen cardiac dyspnea develop while a saline infusion was being given, and the patient had a rising output which reached a peak simultaneously with the onset of the dyspnea. It is important, in considering this subject, to separate hyperpnea from dyspnea. Patients with advanced cardiac disease, but short of the stage at which dyspnea is present at rest, do not usually show much hyperpnea, although they may be breathless on effort During the later stages of the disease, when the cardiac output is low, there is hyperpnea, and its degree is closely correlated with the cardiac output reduction (59)

Edema. A recent article by Warren and Stead (85) has indicated the need for drastic revision of our views on the origin and nature of edema. The distinction between renal and cardiac edema appears to have little basis other than armchair speculation Warren and Stead (86) have shown that there is no significant difference in the protein content of edema fluid in renal and cardiac edema. The venous pressure is increased in both cardiac failure and acute nephritis (52) Nephritic edema may occur first in the feet, and cardiac edema may appear first and most markedly in the face (66) The distribution of edema is therefore determined by laxity of tissues as well as by gravity

While cardiac edema is closely correlated with the raised venous pressure of cardiac failure, there is less certainty that it is the proximate cause of the condition While the experiments of Drury and Jones (27) and Krogh, Landis, and Turner (50) showed that tissue fluid would increase with a raised venous pressure, they did not reproduce all the clinical features of cardiac edema, and the writer has observed (in the course of work with Morris) that pitting edema cannot be produced in a normal limb by pro-

have been studied in this school in cases of atrial septal defect Brannon, Weens, and Warren (8c) have published an excellent study of this condition. They found that the systemic blood flow is within normal limits while the flow through the pulmonary circulation is raised to 10 to 18 liters per minute This seemed to result from a higher pressure in the left auricle (1 to 2.5 cm higher in one case), driving the extra blood through the patent septum into the right side of the heart, where it is added to the systemic inflow. They also indicated that the catheter could be used to differentiate other conditions associated with right ventricular hypertrophy and prominent pulmonary artery These cases form a considerable proportion of patients with congenital heart disease, and cardiac catheterization is a new method of great value in their study When the quantitative data on various forms of congenital heart disease have been fully worked out, much light will be shed on fundamental cardiovascular reactions and the adaptations to various congenital defects

Some General Considerations. The technic of cardiac catheterization is safe and it has come to stay It has a value for research, and its full use in the quantitative study of the fundamentals of heart failure will yield a rich harvest of results. We can envisage its increasing utilization in the routine study of difficult or problematic cases of heart disease, and its use in more ordinary instances to control the action of cardiac drugs seems fully justified

Probably our most illuminating observations have been made in the group of cases with so-called "high output failure" The occurrence of venous congestion, edema and breathlessness in this group casts into considerable uncertainty many widely accepted views on the fundamental nature of cardiac failure The view put forward (57,58) that the high venous pressure is a compensating phenomenon must be accepted for this group. When the heart is pumping blood round the body at twice or three times the normal rate, it cannot be said that blood is being dammed back in the veins. The occurrence of a high venous pressure in anemia with low blood volume seems to establish the necessity of postulating a venomotor mechanism

Cardiac Dyspnea. Some physicians find it difficult to understand how the cardiac output can be normal in a patient with shortness of breath It must be remembered that the measurements are all made with the patient in the resting state. The method has not yet been applied to any extent in studying man during exercise It may be assumed, however, that the cardiac output during exercise of the patient with cardiac failure does not rise as high as that of the normal person, and that in the final stages of

in obstructive jaundice; it seemed possible that an increased intravascular pressure in the liver sinusoids might be sufficient to create a pressure against which bile could not be secreted. The factors (possibly high venous pressure) causing retention of bile to this degree seem to be independent of those (possibly low oxygen tension) causing central degeneration of the liver lobules. By the analysis given by Bolton and Barnard (6) many years ago, a high venous pressure is probably not the cause of the central degeneration of the lobules, as such a pressure would act more on the periphery of the liver lobule.

Acute Hypotension
(Shock, Peripheral Circulatory Failure)

The term "shock" has been used to describe a multitude of different conditions ranging from the remote effects of injury to the acute effects of such profound metabolic disturbances as the crises of Addison's disease and the circulatory collapse of diabetic coma. It is thus no single entity, and since some forms of heart failure have a peripheral origin, arising from the demand for a greater blood flow (see page 78), it is doubtful if "peripheral circulatory failure" is a good term either. As all the conditions included under "shock" are characterized by a low blood pressure, we shall use the term "acute hypotension," which clearly indicates our meaning.

Taking first the condition to which the term "shock" has been most widely applied, namely "wound shock," we may review the situation best by stating simply how our outlook has been modified during the recent war. At the beginning of the war it was thought that wound shock was a result of depletion of the effective volume of blood in circulation. As a result of decreased filling of the heart, the cardiac output is lowered to a level at which cardio-acceleration and vasoconstrictor reflexes no longer "compensate" and the blood pressure falls. This classic concept still holds true, but as a result of much research it has undergone modification, and we may consider *seriatim* the basic points.

Blood Volume Reduction. The view that blood was pooled or trapped in some part of the vascular system has been discarded. It is now widely agreed that hemorrhage is the major factor in shock from war wounds. Hemoconcentration, indicating plasma leakage from capillaries, is not seen except in burns, crushing injuries, and some types of abdominal injury. The efforts made by various experimental workers to reproduce hemoconcentration as an essential factor of shock seem to have been misguided. Much misunderstanding seems to have arisen in the past as to the rate at which blood is diluted after hemorrhage. The work of Wallace

longed venous congestion (60). Further, the rises in venous pressure which are associated with cardiac edema are often very slight; Smirk (75) has pointed out that they are not more than the difference between the venous pressures of a tall man and a short man. Sometimes gross degrees of local venous obstruction may be seen with no more than brawny swelling of the limb. High venous pressures may be present in young people with heart disease for long periods without the appearance of pitting edema.

To explain this discrepancy, the theory of capillary anoxia was brought in. Landis (53) found that deprivation of oxygen for 3 minutes made capillaries more permeable to protein. Although these experiments were beautifully devised, the deprivation of oxygen was too crude to resemble in any way that which might be produced in cardiac failure. If any tissue is unlikely to suffer from oxygen lack, it is surely the capillary wall. Our observations indicate that blood returning to the heart in heart failure is seldom less than 40 per cent saturated with oxygen; this would leave plenty of available oxygen for the wall of the capillary, and would not reduce the mean capillary oxygen tension below 50 mm. Hg as compared with a normal tension of 60 mm. Hg Warren and Stead have envisaged a new concept based on the close correlation between a raised plasma volume and the high venous pressure in cardiac failure. They think that there may be retention of salt by the kidney as part of the process, enabling the organism to raise the blood volume and thus the venous pressure. That this concept needs revision is obvious when we realize that in anemic heart failure the blood volume is often low Sharpey-Schafer (74) has observed volumes as low as 2 liters in the presence of considerable rises of venous pressure While Warren and Stead's hypothesis is of great interest, there is obviously a discrepancy to be explained in these anemic cases If salt retention comes into play at all in the production of edema, it is not necessarily part of a mechanism for increasing blood volume.

The whole problem of edema requires reconsideration on the basis of the new method, combined with studies of tissue pressure and rates of edema formation, in relation to the general circulation rate at the time of the study.

Jaundice in Heart Failure. About half the patients dying of heart failure have a raised serum bilirubin level The normal upper limit is 1 mg. per 100 cc , while in severe heart failure a value around 2 mg per 100 cc is commonly found These cases usually have a very high venous pressure, and in a small number of cases with an excessively high venous pressure, jaundice may be severe McMichael and Sherlock (64) have reported the findings in such a case. The pathologic picture closely resembled that

output falls, the pulse is accelerated, and the peripheral resistance is increased. After this first phase, however, further reactions may develop which are somewhat unexpected. The blood pressure, which was at first maintained, gives way and falls to levels of the order of 60 mm Hg. The

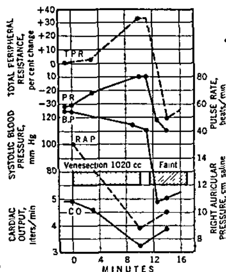


Fig 18 Faint induced by venesection (2) Arterial pressure is first maintained by peripheral vasoconstriction (increased total peripheral resistance) in spite of a falling cardiac output After the end of venesection the subject fainted and during the faint the cardiac output increased slightly, fall in blood pressure was therefore due to decrease in peripheral resistance

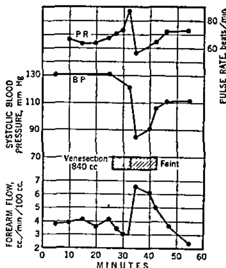


Fig 19 Faint induced by venesection (2) During the faint, muscle blood flow underwent a great increase which passed off with recovery

pulse, after initial acceleration, falls from 90 to 40 to 50 per minute. This *vasovagal reaction* is due to a sudden vasodilatation in the arterioles of the skeletal musculature (Figs 18 and 19) The peripheral vasodilatation is mediated by autonomic nerves, since the reaction can be abolished in the forearm muscles by blocking the main nerves at the bend of the elbow with novocaine (2)

This reaction, though resembling an ordinary faint induced by emotion, seems to bear some relation to the volume of blood lost. Its incidence rises from about 4 per cent among blood donors bled 420 cc to 40 to 50

and Sharpey-Schafer (84) has made it clear that full blood dilution is not reached until some 40 hours have elapsed after the loss of 1,000 to 1,200 cc. of blood. The usual degree of dilution seen an hour or two after severe blood loss is seldom more than 15 to 20 per cent, i e , the hemoglobin is reduced to 80 to 85 per cent of the original value. Posthemorrhagic anemia is thus not recognizable by simple hemoglobinometry until two or three days have elapsed. In World War I these phenomena of bleeding were not generally appreciated, though the importance of hemorrhage as a cause of shock was recognized by Keith and a few other clinical observers.

The quantitative estimation of blood volume reduction after hemorrhage is still beset with difficulties It is reasonably certain that in some cases 60 per cent of the blood volume may be lost but that such patients may recover after massive transfusion. Dyes which are used for blood volume estimation are admittedly lost from the circulation, and the rate of loss is variable in cases of traumatic shock (8) The dye method may overestimate the blood remaining in circulation after hemorrhage, and it has been shown that it overestimates blood volume even in the normal subject (46)

Using a concentrated corpuscle method, McMichael, Sharpey-Schafer, Mollison, and Vaughan (61) found that blood volumes are often severely reduced in chronic anemia, which was subsequently found to be associated with an *increased* cardiac output (74). This *hyperkinetic* circulatory state may develop about 24 hours after a hemorrhage, and in fact it is very frequently observed in patients admitted to the hospital with gastrointestinal bleeding From this series of observations, it is clear that while *acute* reduction of blood volume may induce shock, slower reduction (subacute or chronic) leads to no such state If there is recovery from the initial collapse after hemorrhage, the hyperkinetic state may ensue in a matter of hours The mechanism of this circulatory adaptation to a low blood volume is not understood, but it does open up the possibility of a pharmacologic approach to the problem of treatment of hemorrhagic shock.

Cardiac Output and Peripheral Vascular Resistance. The catheter technic for determining cardiac output has also rendered possible a quantitative estimation of peripheral arteriolar resistance Mean arterial pressure (B P.) is proportional to the resistance to flow imposed by arteriolar tone (T.P R.) and also to the volume of blood ejected into the arteries in unit of time, or the cardiac output (C O) Thus B P $\propto$ C O $\times$ T.P R. If B P. and C.O are known, T P R changes can be followed.

In hemorrhage, the initial changes indicated by the classic concept are confirmed: the pressure falls in the great veins near the heart, the cardiac

of shock produces final dissolution as a result of diminished oxygen transport to the tissues. It was believed that oxygen therapy might find a place in increasing slightly the amount of available oxygen in each unit of blood reaching the tissues. This expectation has not been fulfilled, and a paper by Frank and Fine (36) gives much food for thought. Dogs put into shock by bleeding were given oxygen even under high pressure (up to 3 atmospheres). By this means it was hoped to compensate for any deficiency in oxygen supply due to sluggish blood flow. Yet the survival rate of the animals was uninfluenced, and the oxygen uptake by the tissues could not be increased. It seems likely, therefore, that considerable areas of the vascular bed are completely shut off in profound shock, a condition which was demonstrated many years ago in bled animals by Rous and Gilding (70).

Burns and crushing injuries produce a similar sequence of events in the circulation by causing acute reduction of the blood volume as a result of plasma leakage The clinical picture in each case is complicated by the fact that there is a profound metabolic disturbance as well as the circulatory disorder, but detailed discussion of the metabolic consequences is beyond the scope of this review.

When injury is complicated by bacterial invasion with toxemia, another shock-producing factor is introduced The factors concerned here still require close analysis by modern methods Richards (68) has shown that in abdominal wounds, when infection is a frequent complication, the cardiac output is very low in relation to the blood volume, which is only slightly reduced. This suggests either that the heart is directly damaged by the bacterial poisons, or that the mechanisms regulating cardiac filling during diastole have broken down Richards' right auricular pressure measurements suggest that the latter mechanism is responsible.

In a study of circulatory collapse complicating acute infections, Ebert and Stead (28) found that the venous pressure was lowered. In a case of cholecystitis with spreading peritoneal infection, the writer and Dr. Sharpey-Schafer found that both the venous pressure and the cardiac output were low, and that the latter could be raised by a saline infusion This observation fits in with the previously recorded findings quoted In patients who have died of bacterial toxemia Rich (67) has shown that the cortex of the adrenal gland has undergone degeneration

This raises the question of what the adrenal cortex has to do with the maintenance of vasomotor and venomotor tone Now that the work in this school has shown that in anemia the blood volume may be low with a high cardiac output, the usual explanation given for the circulatory col-

per cent of those bled a liter or more (2). Most reflexes seem to be protective, and a purposive interpretation can usually be offered; if the vasovagal reaction is indeed a reflex, its usefulness to the bled individual is difficult to appreciate. The reaction may even be precipitated during anesthesia in an injured person, especially when a fracture is manipulated. Placing a wounded soldier in the sitting position may also induce a vasovagal faint. It has even been suggested that vasovagal syncope may be fatal; while this is possible, it is difficult to substantiate, as we know little of the meaning of slow heart rates in the moribund.

Recognition of vasovagal collapse is easy if the slow heart rate is observed. Recovery in mild cases will occur when the recumbent or head down position is adopted. Methedrine (*N*-methylphenethylamine), 20 mg. intravenously, or 30 mg. intramuscularly, accelerates recovery. In those who recover without drug treatment, the pulse often remains slower than would be expected for the degree of blood loss. Thus the vasovagal factor may complicate and modify the classic picture of oligemic shock. Perhaps this point is best illustrated by a case observed by the writer in 1944.

Following a flying-bomb incident, a middle-aged woman was admitted to the hospital with injuries from flying glass, including deep cuts from which blood loss had been considerable Two hours after the injury the arterial pressure was 65/40 mm Hg and the pulse rate 80 per minute. The heart rate was thus unexpectedly slow in relation to the blood pressure. She was given 20 mg. methedrine intravenously, after which the blood pressure rose to 90/60, the pulse to 110. It seems possible that methedrine abolished the vasovagal component and restored the "classic" state of affairs

Vasodilator factors in the condition following injury are certainly being more widely appreciated. Richards (68) has shown that, in the average case of shock, the cardiac output seldom falls below 3 liters per minute Yet this degree of cardiac output reduction may be reached in simple mild hemorrhage and the arterial pressure may remain high as a result of compensatory vasoconstriction—see Figure 18 (just before the faint). Vasoconstriction thus seems to be inadequate when the fully developed shock picture is present In other words, the deep fall in blood pressure is due more to lack of vasoconstriction than to a further fall in cardiac output It is not suggested that the vasovagal reaction is always the responsible vasodilator mechanism, other factors, such as infection and tissue trauma, with local or general vasodilator effects may come into play, but as yet these influences are poorly defined

Tissue Anoxia. It is generally thought that the circulatory failure

drops below 7 grams As the patients recover, the raised pulse rate returns to normal and the cardiac output falls. Sharpey-Schafer (74a) has shown that in severe anemia transfusion raises the right atrial pressure and that this is accompanied by a *fall* in cardiac output. Such a reaction can only be interpreted as an overloading of the heart. A similar observation in a case of aplastic anemia may be seen in the data of Brannon *et al.*

The same workers (8b) also report on 13 patients with low blood pressure following hemorrhage In some instances the cardiac output was down to 2.7 liters per minute, but in others it was within normal limits, or even high. In those with high outputs, the hemoglobin was reduced to anemic levels. The lowest hemoglobin level was 9 3 grams per 100 cc., so that a high output occurred at a higher hemoglobin level than in chronic anemia. This difference between chronic anemia and the condition following hemorrhage can also be seen in Sharpey-Schafer's data (74) Brannon and his co-workers agree that circulatory failure from hemorrhage may be complicated by vasodilatation similar to that seen in the common faint

In patients with chest wounds Merrill *et al.* (64b) find that the cardiac output is more often normal or high, in spite of a low blood pressure. The latter must therefore be due to vasodilatation. They invoke the muscle dilatation of fainting as a possible explanation Survey of their data shows that in some of the cases there was probably decreased oxygen saturation of the arterial blood, such lowered oxygen tension is known to be a factor in the production of high cardiac outputs, as discussed on page 78.

Pericardial Disease

Warren *et al.* (84b) have observed patients with stab wounds of the heart and with pericardial infection They found that the cardiac output rises when the high right atrial pressure is further raised by saline infusion. In most of their cases the cardiac output was lower than in the case studied by Fletcher (35), but they give no data on the pericardial pressure. Lyons and Burwell (55a) report further observations on constrictive pericarditis with cardiac output changes, studied by the acetylene method Intravenous infusions and venesection resulted in gross changes in the venous filling pressure, but they failed to produce any changes in the cardiac output. *Atropine, however, apparently increased the cardiac output.* All these data seem to confirm the conclusion already given, namely, that in constrictive pericarditis the stroke volume is almost unalterable

Theophylline Ethylenediamine

Howarth *et al.* (46b) report that the theophylline component of this substance is responsible for its circulatory action, very rapidly lowering the

lapse of the crisis of Addison's disease, namely, a low blood volume, will have to be reconsidered. The observations of Richards and of Rich, at any rate, open up the possibility that the impairment of venomotor tone in overwhelming infections may be mediated at some point in the chain of events by a mechanism involving the adrenal cortex.

Other types of shock occurring in civil medicine are worthy of detailed investigation by the new cardiac output method

The fall of arterial blood pressure in coronary thrombosis with myocardial infarction has not yet been satisfactorily explained. Fishberg, Hitzig, and King (33) found diminished blood volume in one case, but this does not seem to be a satisfactory explanation, as other cases did not show this change In any case it would be difficult to account for any loss of blood unless we invoke the now discarded theories of blood pooling in shock states We have only had the opportunity to study one patient (63, Case 10) who was in heart failure from previous coronary occlusions and was moribund. At this stage the cardiac output was low normal (4.3 liters) and the low blood pressure (80 mm. Hg) was therefore due to peripheral vasodilatation. Condorelli (19) found that occlusion of the left coronary artery of the dog caused a fall in aortic pressure, but that this did not occur if the vagus and sympathetic nerves on both sides were cut It may be that the fall in pressure is due to reflex vasodilatation, Fishberg and his associates (33) did find the venous pressure to be low at the stage of hypotension. As in so many other fields, we should prefer to see much more work with the cardiac catheter before giving a final opinion.

Diabetic coma also produces a particularly fatal type of low blood pressure Studies on the blood in the femoral vein by Schecter, Wiesel, and Cohn (72) indicate that the blood flow through the limb is either rapid or the oxygen uptake by the tissues is impaired Our experience shows that in diabetic acidosis the oxygen uptake is normal, or even raised, and we favor the view that the cardiac output is increased with accompanying vasodilatation in the early stages The later sequence has not yet been worked out.

Addendum

Other studies on cardiac catheterization have appeared since this report was written As they add to and amplify the work already described, they will be briefly reviewed here

Anemia, Hemorrhage, and Shock

Brannon *et al.* (8a) find that in chronic anemia there is no significant change in the minute volume of the circulation until the hemoglobin level

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raised venous pressure in congestive failure. The rise in cardiac output is partly the result of this reduction in venous pressure, partly that of a direct stimulating action on the myocardium. The drug produces a greater rise in cardiac output in hypertensive heart disease than in mitral stenosis. It may be administered intravenously as a useful adjuvant to digitalis therapy, especially in hypertensive heart failure.

Edema

A most important study of renal function in cardiac edema by Merrill (64a) throws further light on the mechanisms involved. When, in heart failure, the cardiac output is reduced, the renal blood flow drops to about 30 to 20 per cent of normal In other words, the reduction in the renal blood flow is greater than in the general circulation. However, reduction in renal blood flow is closely correlated with reduction in cardiac output. Thus, while in normal subjects 1 2 per cent of the filtered sodium is excreted, patients with heart failure excrete only 0.01 to 0.04 per cent, which shows the considerable sodium retention that occurs in heart failure.

Merrill states that renal blood flow is diminished in anemia, which would mean that the kidney does not share in the generally increased rate of circulation in this condition. Merrill's work seems to answer partially the criticism of the Warren-Stead hypothesis outlined on page 90, although the occurrence of edema in generalized Paget's disease with high circulation rate still remains to be explained Though there may be active retention of sodium by the kidney tubules, this retention is not a simple mechanical consequence of diminished renal blood flow.

Rise of Venous Pressure in Heart Failure

Landis *et al* (53a) have studied the effect of experimental heart failure on venous pressure. In the normal dog exercise reduces the venous pressure, after ligation of the right coronary artery, the venous pressure remains unchanged at rest, but rises during exercise. Auricular fibrillation does not cause venous pressure to rise, but exercise added to fibrillation will raise the venous pressure In the normal dog, a considerable increase in blood volume will not maintain a high venous pressure.

From these observations it would appear that a rise of venous pressure during exercise is probably an earlier manifestation of impaired cardiac activity than a rise in resting venous pressure. Landis is against the view that plethora entirely accounts for the venous pressure rise in heart failure, but he recognizes peripheral vasoconstriction as an important factor

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vein, then the artery (after the substance had passed through the heart), and immediately thereafter the vein again.

Angiocardiography was first practiced by introducing a catheter into an antecubital vein and passing it into the right auricle. Egas Moniz, in particular visualized the pulmonary circulation in this way. In 1938, Castellanos, Pereiras, and Garcia injected neo-iopax directly into an antecubital vein in infants suffering from congenital right-to-left intracardiac shunts, and demonstrated pulmonary stenosis as well as transposition of the great vessels A year later Robb and Steinberg successfully demonstrated the cardiac chambers and great vessels following the intravenous injection of a 70 per cent diodrast solution. They showed the practical possibility of the method in most individuals and suggested the value of determining the roentgenologic topography of the heart and great vessels in thoracic disease Since that time, together with M. F. Steinberg, we have made a systematic study of various diseases in which the cardiovascular system is either primarily or secondarily involved. We have also, as well as Taylor and McGovern, critically analyzed the normal roentgenologic topography of the heart

Procedures

Angiocardiography. All recent workers have essentially followed the procedure of Robb and Steinberg The only available material for injection which is both nontoxic in the amounts that must be used and at the same time radiopaque is 70 per cent diodrast (Winthrop). To make the injection, an antecubital vein is exposed through a small incision and a 12-gage needle with a stopcock unit (supplied by Becton-Dickinson) is tied into the vein Although it is possible to introduce the needle without making an incision, the results are not as certain, and there is some possibility of untoward reactions as a result of perivascular infiltration The amount of diodrast used in adults is 35 to 45 cc , in children the dosage is smaller (8 to 25 cc), approximately in proportion to weight but not less than 20 cc except in infants

The patient is placed in front of the recording apparatus, in a standing position if his clinical condition permits He is then positioned and the arm to be injected is raised above the head The patient is requested to expire forcibly and during the following deep inspiration the solution is injected as rapidly as possible, not more than 1 5 seconds being taken to inject 40 cc During the roentgen exposures, which include visualization of the aorta, the patient is asked to hold his breath In patients with normal circulation time the exposures are begun when the last 5 to 10 cc

A Discussion of Angiocardiography and Angiography

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Introduction

The term "angiography" is applied to the visualization of blood vessels following the introduction of a contrast substance. When the cardiac chambers, the aorta, and the pulmonary artery are visualized following the intravenous injection of a radiopaque substance, the procedure is known as angiocardiography

An excellent review of the subject of angiography by Camp and Allen is to be found in *Diagnostic Roentgenology.* It will therefore suffice to present here only the important developments in this field Roentgenologic visualization of the blood vessels in pathologic specimens has been performed almost since the discovery of x-rays Usually a barium or bismuth preparation was used for the purpose Arteriography of peripheral arteries in the living subject has been described by Allen and Camp, as well as by dos Santos and Fariñas Cerebral arteriography is now a generally performed procedure; it has been adequately presented by Egas Moniz and his associates, by Lohr and Jacobi, by Gross, and recently by List, Burge, and Hodges Visualization of the abdominal aorta has been illustrated most effectively by Fariñas

The peripheral veins may be visualized either following intra-arterial injection or by direct injection Some years ago Allen and Barker described the former method in detail At the present time, direct injection is the method in common use A most extensive report on this method is that of Bauer. Recent reviews of the clinical value of venography in the diagnosis of venous thrombosis have been made by Allen, Linton, and Donaldson, as well as by Neuhof and Sareson, and Barber and Orley have paid particular attention to varicose disease

Horton has demonstrated arteriovenous fistulas by means of arteriography In some instances the fistula can be shown by injection of the adjacent vein; we have been able to inject an antecubital vein in a case of subclavian arteriovenous fistula in a child, and demonstrate first the axillary

could be interpreted more correctly, since serious error can result from a misinterpretation of what may be only a transient state We have therefore used, successively, fluoroscopy, photography of the fluoroscopic screen—both by a motion picture camera and by a rapid "still" camera—and a wheel mounting 8 cassettes which is rotated by hand The apparatus used at present (Fig. 1), designed and made by Dr. S Feitelberg, consists of a device for 5 cassettes, each one 10 by 12 inches and protected by a layer of lead 1/32 inch thick behind the back intensifying screen of each cassette. The cassettes are lined up on an inclined plane at such an angle that they just tend to slide forward The first cassette stands just in front of the inclined plane and is prevented from falling by a small, electro-

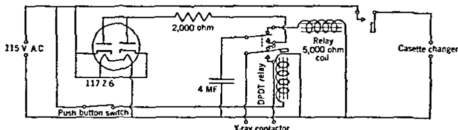


Fig 2 Electric circuit used with apparatus depicted in Figure 1 Pressure on push button makes the exposure; release of pressure causes withdrawal of plunger and exposed cassette drops into protected chamber

magnetically controlled plunger When the plunger is withdrawn, the cassette drops into a lead-protected container, with a floor inclined at such an angle that the cassettes tend to slide away. The second cassette slides into position but is prevented from falling by the plunger which has returned to its original position Controlled motion of the cassettes is assisted by a parallelogrammic arrangement of rods. With this apparatus exposures are made before the cassette moves, rather than after it has reached a certain position The plunger and exposures are controlled electronically (Fig 2) At present, the time of the exposure in relation to the injection is recorded on the film by a radiopaque pointer controlled by a synchronous motor, but the circuit is being modified so as to make exposures in predetermined phases of the cardiac cycle

Schwarzschild, in 1943, described an ingenious arrangement for the successive exposures of 10 by 12 inch cassettes

of the solution are entering the vein, and they are completed in about 8 seconds. The roentgen technic in angiocardiography is that usually employed for demonstration of the heart, but it is advisable to increase the intensity of radiation by about 25 per cent, preferably by adding kilo-voltage.

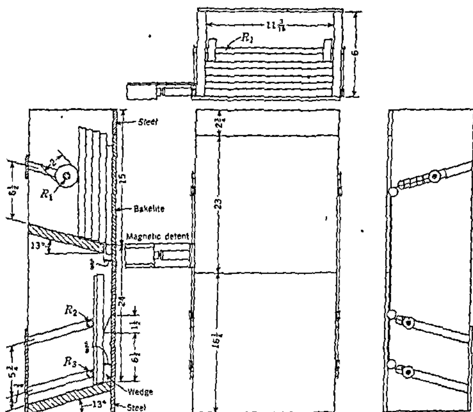


Fig 1 Apparatus for multiple roentgen exposures Five cassettes are arranged on an inclined plane and each one, after exposure, falls into a protected chamber

Several types of recording apparatus have been described in the literature Robb and Steinberg employ a stereoscopic cassette changer, which has the advantage of permitting the use of 14 by 17 inch films but the disadvantage that only 2 exposures can be made at a minimum interval of 3 seconds But it seemed to us and M F Steinberg advisable to make many exposures of the cardiac cycle so that the various opacities

Cinematography of the fluoroscopic screen in human angiocardiography has been achieved with the following exposure factors: 85 kv. (single phase), 150 ma; 2 exposures of 3 seconds each; x-ray tube–screen distance, 27 inches; rotating target tube, 2 0 mm. focal spot.

At first, a Patterson fluorazur screen was used, and an Eastman "blue-sensitive" film; later, a Patterson B screen, with an Agfa "green-sensitive" film The camera used was a Bolex motion picture camera, equipped with an f 0 85 lens, standard camera speed being 20 frames per second with a possible speed of 36 frames in some cases.

The technic used for rapid multiple photographs of the fluoroscopic screen was as follows: 85 kv. (single phase), 150 ma.; x-ray tube–screen distance, 30 inches; screen, Patterson B fluoroscopic; film, Eastman or Dupont single-coated 35 mm., camera, a Leica or Robot, f 1 5 lens. Exposures were made every half second, each 0 2 second on the average Arrangements for using 70 mm. roll film, the 4 by 5 inch photofluorograph, or an automatic camera such as used in aviation photography are simple to set up

At present, the primary aim of the procedures under discussion is the anatomic delineation of the large blood vessels and the chambers of the heart A secondary objective is to record the passage of the medium with sufficient continuity so that the dynamics of the circulation can be studied Extended experience has served to emphasize that single exposures, since they record the state of the chambers and vessels only at the instant of exposure, may give rise to serious misinterpretation We are convinced, therefore, that successive exposures are necessary. In cases requiring sharp outlines direct roentgenography is the method of choice, but roentgenocinematography is to be preferred when physiologic studies require continuous recording

Arteriography. The following technic, as described by Camp and Allen, is the one we have followed without modification.

Upper Extremities The patient lies on the roentgenographic table with the film

tized, and the brachial artery is entered with an ordinary venipuncture needle attached to a syringe containing radiopaque material As soon as the point of the needle is well within the lumen of the artery and bright red blood pulses forcibly into the barrel of the syringe, the sphygmomanometer cuff is rapidly inflated to a point above the systolic blood pressure and the radiopaque material is injected *The needle is withdrawn quickly and, as pressure is applied over the point of punc-*

Essentially, the apparatus consists of three compartments arranged in a straight line The front board of the device extends beyond these compartments to accommodate a thrust bar and a pivoted mercoid switch. The bar is slotted and moves through guides so arranged that it is limited for each extreme of its motion. The pivoted back of the mercoid switch bears a curved extension piece which rests on the thrust bar. When the thrust bar is pushed in all the way, the mercoid is tilted by the weight of the extension piece so as to open its circuit. When the thrust bar is withdrawn, the mercoid contact, which is connected with the x-ray timer, closes.

The device operates as follows The cassettes are stacked in the magazine compartment in front of the pressure block. The patient is positioned with the help of a fluoroscopic screen and the controls are adjusted for radiography. The thrust bar is pushed in, moving a cassette into position in front of the aperture. The contrast substance is then injected into the patient's vein When the thrust bar is withdrawn, the pivoted mercoid switch closes the circuit, which operates the x-ray timer and makes an exposure With the thrust bar fully withdrawn, the spring pressure on the cassettes in the magazine causes the pile to move forward along the metal rails, so that on the next inward thrust of the bar another cassette is moved into exposure position, pushing the previous cassette into the receiver compartment.

In routine angiocardiography it is best to place the patient in the erect position, for in this position the heart is least distorted and obscured by the diaphragm If the condition of the patient precludes the erect position, a horizontal apparatus for multiple exposures becomes desirable Neuhauser and Jennings describe such an apparatus—a simple wooden box in which 8 cassettes 11 by 14 inches rest on 4 bedsprings, each cassette being pushed aside by hand after exposure

When a film 7 by 8 5 inches is large enough to include the part of the heart to be studied, a standard polygraph for 14 by 17 inch films can be used, and 4 successive exposures are possible This film size, however, is ordinarily not large enough except for children or for visualization of a specific part, such as the superior vena cava.

Direct roentgenography, as just described, produces results with the sharpest detail, but the use of large cassettes necessitates large or complicated apparatus to contain and move them This led to the development of indirect roentgenography—photography of the fluoroscopic screen The films are small, so that they may need magnification for study or reproduction Furthermore, the detail is not as clear because the grain of the fluoroscopic screen and of the photographic emulsion may interfere On the other hand, the apparatus is as a rule small and easy to operate

from the film. Head and shoulders must be immobilized. The external carotid is closed off by a rubber strip; the needle–tube–syringe combination is filled with the injection material; the needle is inserted at the carotid bifurcation with the point directed toward the orifice of the internal carotid, and about 10 cc. of contrast material are injected. (Many workers, including List, use thorotrast; others, for example Gross, use 50 per cent diodrast. Convulsions are likely to occur with diodrast, but they are ordinarily transient.) In the lateral position 2 exposures are made as rapidly as the cassette can be changed, the first when the injection is two-thirds complete and of about 1 or 2 seconds. In our experience, which coincides with List's, the results of short exposures of a fraction of a second are not as good as those of the longer ones suggested. A second exposure, to record venous return, can usually be made within 3 seconds after injection is completed

List and co-workers make a second injection in an identical manner, but shift the tube for stereoscopy They also make a third injection with the head rotated to the anteroposterior position For this, the x-ray exposure is begun immediately after the injection starts and no attempt is made to obtain a venogram

Visualization of the vertebral arteries is achieved by retrograde injection of 10 to 15 cc of contrast solution into the subclavian artery. Partial escape of the opaque material into the carotid system may occur

Aortography. Blind puncture of the abdominal aorta in the paravertebral region has been practiced by dos Santos but was not generally used because of the presumed danger Recently Wagner has used this method with no untoward results Fariñas punctures the femoral artery at Scarpa's triangle His procedure is to introduce a radiopaque no 7 or 8 urethral catheter to the desired level of the aorta The patient is then placed in position according to the organ to be visualized so that its selective arteriogram may be made A tourniquet is applied at the root of the opposite member, in order to compress the femoral artery and obtain stasis in the abdominal circulation The contrast medium (20 to 30 cc. of 70 per cent diodrast) is injected within 2 to 3 seconds through the catheter, and an exposure is rapidly made with the aid of a Potter-Bucky diaphragm With this technic a selective study of the circulation of any abdominal organ can be made by placing the end of the catheter close to the point at which its artery leaves the aorta Fariñas reports no untoward results from this procedure, and in his paper includes a number of illustrations of deformity, compression, and stenosis of branch arteries due to tumor

ture to stop any transient leakage, the first exposure is made. The cuff is then deflated quickly to the level of the diastolic blood pressure for a period of 2 to 4 pulse beats so that the injected material can be carried more distally, then reinflated quickly to its previous pressure and a second exposure is made. The procedure is repeated a third time, the cuff is removed, and with a gauze sponge firm pressure is applied over the point of puncture for a few minutes. Additional exposures, with the forearm in pronation or in the lateral position, may be made before the cuff is finally deflated

Lower Extremities The skin and tissues about the femoral artery, just below the inguinal ligament, are anesthetized, the artery is punctured in the same manner as the brachial artery, the lumen is occluded above the point of puncture by pressure of an assistant's fingers, the medium is injected, and an exposure is made The assistant lessens the pressure on the artery, allowing a small amount of blood to flow, occludes it again, and a second exposure is made The procedure is repeated for a third roentgenogram

In the case of arteriovenous fistula, the first exposure must be made as rapidly as possible after the contrast medium is injected, and it is usually advisable to maintain occlusion of the injected artery until 3 exposures have been made

The contrast medium of choice for arteriography is thorotrast, a colloidal thorium dioxide suspension For the upper extremity 5 to 12 cc are used, a larger amount being required for the lower extremity. Volumes in excess of 20 cc , however, should be avoided There is practically no immediate reaction; delayed effects will be discussed on page 112 Ethyl tri-iodostearate has been used in Germany as a contrast medium, and reputedly has many advantages, but at the present time it is not available here Some workers have used the organic halogens However, their use is not advised, since they carry with them the danger of arterial spasm, associated, although rarely, with gangrene of the extremity

Cerebral Arteriography. List, Burge, and Hodges have recently reviewed the literature on this procedure In most cases the carotid artery on one side is injected; when it is necessary to include portions of the brain, the blood supply of which is derived from the vertebral arteries, the site of injection is modified accordingly

Carotid angiography is performed as follows The carotid bifurcation is exposed under local anesthesia, segments of the common, internal, and [illegible] the [illegible] ans- [illegible] head [illegible] is turned toward the unoperated side, the side to be injected being farthest

permits visualization of the axillary and subclavian veins. Venograms of the external jugular and median cephalic veins are made following injection at a point distal to the part under study.

Toxic Effects of Commonly Used Radiopaque Substances

Diodrast. In general, diodrast is a very satisfactory medium for venography. It causes little venospasm; systemic reactions are usually minimal; flushing and a sense of warmth are common, but transient; nausea, vomiting, urticaria, itching, sneezing, and a sense of laryngeal constriction occur occasionally, but they are rarely of sufficient moment to cause any concern. In the few instances in which it has been necessary, administration of 0.3 to 0.5 cc of 0.1 per cent epinephrine has afforded prompt relief. The literature records syncope and shock as a result of diodrast injection, both responding to epinephrine. Toxic reactions supposedly occur chiefly in cases where renal damage is present. Although some authors feel that azotemia is a particularly predisposing factor in diodrast reaction, our experience has not convinced us that this is the case except when there is other evidence of severe renal damage.

The report of Pendergrass *et al.* on unfavorable sequellae following injection of contrast mediums spread considerable alarm. In their report they analyzed questionnaires covering 661,800 urographic examinations; 26 deaths were attributed to the medium, 10 being classified as immediate and 16 as delayed. Previously, 11 fatalities had been recorded in the literature, of which 7 were immediate and 4 delayed. Apparently, the delayed deaths occurred in individuals with severe systemic disease and might perhaps be attributed to pre-existing major renal damage. It is advisable, therefore, not to inject the organic halogens in the presence of severe renal damage or to patients with marked jaundice. Pendergrass *et al.* consider the immediate deaths to be due to a drug hypersensitivity or idiosyncrasy, or to colloidal shock. Their data, however, do not demonstrate conclusively that the reaction is allergic in type. Severe reactions have been reported when contrast mediums were injected repeatedly. Of course, the fact that such reactions may occur demands that the injection be made by a physician and that epinephrine and other cardiorespiratory stimulants be readily available.

Patients should be questioned closely regarding their history of allergy, with special attention to asthma, hay fever, rose fever, drug sensitivity, and eczema in childhood. Not only the individual's history, but that of the family as well should be investigated. When a positive history is obtained, it is our practice to review the need for the examination. If it is at

Direct Venography. Bauer's description of direct venography as applied to the deep venous system of the calf is classic, and we have followed his technic, generally speaking. Bauer points out that the leg veins and most of the thigh veins are portrayed best if the opaque medium is injected through the small saphenous vein. If a cutaneous incision 1 to 2 cm in length is made about 1 cm. behind the lateral malleolus, a vein about the thickness of a lead pencil will be found running vertically in the subcutaneous tissue. This vein, which is the most important tributary to the small saphenous vein and which also communicates by powerful anastomoses with the deep main veins of the lower leg, ought to be selected for the injection.

The injection of 20 cc of 35 per cent diodrast is made continuously and evenly through 60 seconds; if there is resistance, the time of injection may be lengthened to 70 to 80 seconds. An 18-gage, ball-pointed needle helps to maintain slow injection. We have found that if at the end of 40 seconds an exposure is made in the anteroposterior position of the calf, it is possible to turn the leg into the lateral position in time to make a second exposure at the end of the injection. The second view can be of considerable value in interpretation. In the anteroposterior view the leg is held in slight inward rotation, in order to spread the tibia and fibula apart. For both exposures the heel rests on a wooden block, to relieve pressure on the veins of the calf.

Welch and co-workers state that in cases of previous deep phlebitis there is a preferential passage of diodrast through the long saphenous vein. They therefore modified Bauer's technic by applying a blood-pressure cuff with a pressure of 20 mm of mercury to the lower leg, the upper edge of the cuff being placed at the midcalf. This procedure, they believe, will prevent passage of the diodrast through the long saphenous vein.

For visualization of the common femoral iliac veins or the vena cava Bauer advises rapid injection (5 seconds) of 20 cc of 50 per cent perabrodil into the large saphenous vein in the upper thigh. It has been our experience, however, that injection as rapidly as possible of 20 cc of 35 per cent diodrast into the vein behind the external malleolus results about 5 seconds later in very satisfactory visualization of the femoral and iliac veins.

Camp and Allen point out that when visualization of the veins proximal to the point of injection is desired, the injection should be made into the long saphenous vein or one of its tributaries in the lower part of the leg. This includes the superficial system of the calf, the upper segment of the saphenous vein, and the upper femoral and iliac veins.

In the upper extremity, injection of the median basilic vein at the elbow

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all possible, we abstain from using the contrast medium, but when the procedure is considered essential we proceed with it. Occasionally, a prophylactic dose of 0.3 cc of 0 1 per cent epinephrine is used, particularly if the patient is one who has shown a mild reaction during intravenous urography in the past. This has been effective in preventing untoward results, in our experience.

The 1941 issue of "New and Non-Official Remedies" advises that contrast mediums should be used with caution in pulmonary tuberculosis, hyperthyroidism, and where a reduction in blood pressure would be dangerous. From the literature it is not very clear why such advice is given We ourselves have not observed unusually severe reactions either in pulmonary tuberculosis or hyperthyroidism

A number of tests for sensitivity to the contrast mediums have been devised, but there is no conclusive evidence that any of them will sort out those patients who will react badly to the intravenous injection An ocular test is used by Archer and Harris, who place a drop of the material on the conjunctiva, but some opthalmologists feel that a severe reaction is not without danger to the eye We use, routinely, the skin test devised by Robins This consists of the intradermal injection of 0 05 cc of the contrast material, and examination 10 to 15 minutes later of the size of the wheal and erythema. We use the test largely for medicolegal reasons, since in our experience there has been no definite correlation between the severity of the skin reactions and the systemic effects of intravenous urography

In angiocardiography our practice is to inject 1 to 2 cc of the contrast material intravenously, preliminary to the full injection, and proceed if there is no reaction in 5 minutes When the patient is known to be an allergic individual, a prophylactic, subcutaneous injection of epinephrine is given In no case is more than one injection of diodrast permitted in this type of patient

Thorotrast. Many workers strongly advise against the use of thorotrast as a constrast medium because of its very slow excretion It is retained in the reticulo-endothelial system for many years, and it has been thought that its measurable and long-lived radioactivity might be a source of danger (except, of course, in patients with a short life expectancy) Last *et al*, however, offer convincing data as to the lack of danger when reasonable amounts of this substance are used They point out that the beta and gamma radiations are negligible The alpha radiation from 25 cc. of thorotrast is of the order of 0 5 to 1 0 microgram of radium, whereas the lowest recorded rate of activity observed in bodies of patients with

demonstrable radium poisoning is that equivalent to 2 0 micrograms of the element These authors also determined, by postmortem examinations, that the total measurable ionization in the liver and spleen following injection of 30 cc of thorotrast was 4 89 microcuries, which is definitely below the lowest level observed in radium poisoning While they admit that the possibility of long-delayed radiation damage cannot be completely excluded, clinical experience, which in the hands of Egas Moniz now stretches over 13 years, speaks against the likelihood of any significant radiation effect. Another possible danger in the use of thorotrast is pointed out by Ekström and Lindgren, who found thorotrast emboli in small vessels in 21 out of 35 postmortem examinations on patients who had received thorotrast for cranial arteriography

Thorotrast is water miscible, highly opaque to x-rays, and essentially nonirritating The alternative substance in cerebral arteriography is 50 per cent diodrast, which is locally irritating, and may produce convulsions However, the contrast is satisfactory and Dr S Gross in the x-ray department of The Mount Sinai Hospital has obtained good results with it

Clinical Applications of Angiocardiography

Differential Diagnosis of Aortic Aneurysm and Mediastinal Tumor. The fact that mediastinal tumors are located in close proximity to the heart and large vessels occasionally makes it very difficult to differentiate the tumors from vascular structures when examined by conventional roentgenology (Figs. 3–8) A tumor may be apposed so closely to the pulsing structure, especially if it is cystic, that it appears to be pulsating actively whether examined under the fluoroscope or with the kymograph Indeed, an audible murmur may be elicited over the appropriate part of the chest, and a diagnosis of aneurysm may seem justified both on clinical and roentgenologic evidence On the other hand, aneurysms do not always pulsate, the reason being either because the wall is thick, fibrous tissue, or because the communication with the great vessel of its origin is small. It is also possible for an aneurysm to be clotted

In The Mount Sinai Hospital angiocardiography is now routinely performed in such cases, except when the conventional roentgenologic examination shows the mass to be clearly separate from the heart and great vessels With proper timing, the pulmonary artery and aorta can usually be completely outlined When the mass is a tumor, the great vessels are sharply and continuously outlined, and there is a uniform decrease in their size as the vessels are traced from their origins An aneurysm, on the other hand, becomes opaque at the same time as its vessel of origin, a de-

luscence in the wall of the vessel may be seen, and there may be local dilatation of the vessel at the aneurysm or elsewhere. Angiocardiography is not infallible; clotting in the aneurysm or the smallness of its com-

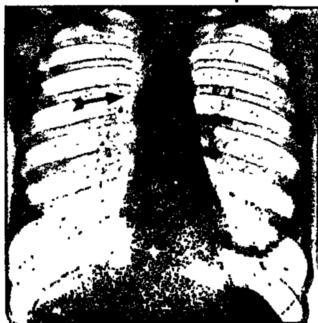


Fig 3 Teratoma of anterior mediastinum Tumor mass (black arrows), aorta, normal in caliber and outline (white arrows)





munication with the vessel of its origin may prevent the diodrast from filling the aneurysm, or the material may not enter in sufficient concentration to be detectable

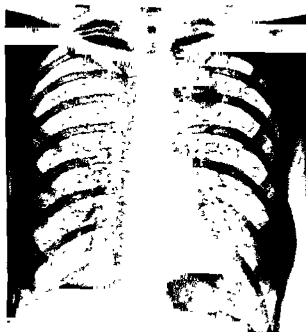


Fig 4 Congenital, multiloculated aortic aneurysm (black arrow) opacified together with aorta (*white arrows*) *Right* anterior oblique view below







Fig 5 Actively pulsating dermoid cyst of anterior mediastinum (black arrow), aorta *normal in caliber and outline (white arrows).*



Fig 6. *Luetic aneurysm of innominate artery (black arrow) opacified together with aorta, dilatation of ascending aorta (white arrow)*



Fig 7. Dissecting aneurysm of innominate artery due to medial necrosis not opacified by diodrast, ascending aorta and arch normal in caliber (white arrows)







Fig 8 Luetic aneurysm of descending aorta (black arrow) opacified with diodrast, ascending aorta of irregular lumen (white arrow)

Obstruction of Superior Vena Cava. Under ordinary circumstances, this condition can be diagnosed clinically without difficulty. Sometimes, however, it becomes necessary to delineate the precise site and length of the obstruction (Fig 9) Many consider a single roentgen exposure after injection of an antecubital vein sufficient, but we have found multiple exposures following the injection to give more desirable results. Because



Fig 9 Thyroid adenoma compressing superior vena cava

of uncontrollable retrograde filling of tributary veins, the superior vena cava may not be fully distended at any given instant On the other hand, this excessive retrograde filling of the collateral circulation is a valuable confirmatory sign of superior vena caval obstruction Dr H. Neuhof has suggested that a catheter be introduced intravenously as far as the obstruction for the injection of the opaque material (following in general the technic of Cournand as applied to right auricular intubation), in order to achieve maximal concentration at this point We are now testing this suggestion, but results to date indicate that what is gained by delivering the opaque material at the point of obstruction is lost by the slowness of injection necessitated by the small caliber of the catheter. Some workers have intimated that untoward systemic effects may occur with this type of injection, but the limited experience of one of us (M L S) has not corroborated this

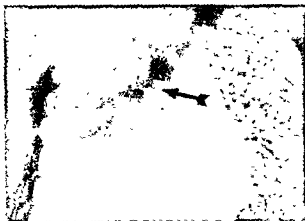


Fig 10 Carcinoma of right main bronchus, constricting superior vena cava at its entrance into the heart

So far, the visualization of the obstructed superior vena cava has only infrequently provided data which could not have been anticipated clinically Pressure by a large tumor mass can be demonstrated, but this usually can also be surmised by other methods However, in one instance an unsuspected infiltration of the left subclavian vein by a tumor was shown, suggesting that wider experience may prove its greater usefulness We are at present investigating the possibility of demonstrating pressure or infiltration of the vena cava by enlarged mediastinal nodes, it is hoped that this may provide information regarding the operability of primary carcinoma of the bronchus (Fig 10) When obstruction of the superior vena

cava follows mediastinitis, visualization demonstrates the site and degree of obstruction and fully portrays the collateral venous pattern (Figs. 11, 12) The method may prove useful in the study and treatment of constrictive pericarditis, when basal adhesions result in an elevated venous pressure.



Fig 11 Luetic mediastinitis with marked constriction of superior vena cava, extensive collaterals Case reported in detail by Zeman



Congenital Heart Disease. The useful information which angiocardiography can provide regarding congenital cardiac lesions depends upon three factors. These are the severity of the anatomical lesion, the ease with which the affected structure is visualized, and the changes that have taken place in the circulatory dynamics For ease of discussion, the lesions may be classified as (*1*) abnormal position or size of a large vessel or chamber outlet; (*2*) right-to-left intracardiac shunt, (*3*) patent ductus arteriosus; (*4*) left-to-right intracardiac shunt

A discussion of clinical diagnosis is outside the scope of this review. But it should be emphasized that angiocardiography is not essential in the diagnosis of most instances of congenital heart disease in adults. Careful clinical examination, electrocardiography, conventional roentgenologic investigation, and such simple tests of circulatory dynamics as blood pressure readings in all extremities, pulse tracings, and blood circulation times ordinarily permit reasonably accurate diagnosis But in infants multiple lesions are the rule, and diagnosis may be impossible even with the aid of angiocardiography, except as to the presence of right-to-left shunt



Fig 12 Constriction of right innominate vein by mediastinal adhesions after thyroidectomy, extensive collaterals

Abnormality of a Large Vessel or Cardiac Chamber Outlet. Angiocardiography affords precise portrayal of the anatomic findings in dextrocardia, right aortic arch, coarctation of the aorta, stenosis of the left subclavian artery, and stenosis of the pulmonary artery. Aortic and subaortic stenoses are not often demonstrable, but associated unsuspected deformities of the aorta are fairly frequently visualized. Stenosis at or near the pulmonary valve, on the other hand, is usually clearly visualized (Fig 13). Congenital dilatation or aneurysm of the aorta or pulmonary artery ordinarily is well defined, and in a few instances an anomalous pulmonary vein ascending on the right side of the chest to enter the hemiazygos vein has been recognized.

In many cases, the information provided by angiocardiography is of academic interest only The diagnosis of right aortic arch, for example, is easily established by signs of pressure on the esophagus, caused by a pulsating "knob" at the level of the aortic arch from the right and posteriorly (Fig 14). But even this condition may be present in a confusing form, since the following variations may occur: (*a*) a so-called diverticulum extending posterior to the esophagus and slightly to the left; (*b*) a rudimentary arch or ventral diverticulum; (*c*) a fully developed left aortic arch in addition to the right, (*d*) a left innominate artery, simulating an isolated transposed arch During life, these variations can be demonstrated and interpreted only by means of angiocardiography

While coarctation of the aorta can be diagnosed by clinical and laboratory means, the precise location, length, and configuration of the coarcted segment has become a matter of practical concern since it has been discovered that the condition is apparently operable (Fig 15, page 126)

Angiocardiography may also be helpful when multiple lesions produce a confusing murmur or a roentgenogram which is difficult to interpret. For example, coarctation of the aorta occasionally occurs in association with aortic or subaortic stenosis This may account for an otherwise inexplicable dilatation of the ascending aorta distal to the stenosis. On the other hand, while the presence of a systolic and early diastolic murmur over the pulmonary area in a case of coarctation might suggest that a patent ductus arteriosus is also present, angiocardiography provides the means of determining its presence or absence

Stenosis of the left subclavian artery deserves special mention here, for angiocardiography has furnished the means of demonstrating this cause of the absence of a left radial pulse (Fig 16, page 127) It has also demonstrated association of this condition with coarctation of the aorta or with a generally small aorta That it is occasionally associated with stenosis of the innominate artery has been suggested by pulse tracings



Fig 13 Congenital pulmonary stenosis, arrow indicates stenosed valve

Fig 14 Right aortic arch (black arrow) in association with tetralogy of Fallot, pulmonary stenosis (white arrow) Simultaneous visualization of pulmonary artery and aorta



A Conventional roentgenogram, postero-anterior view.
B Angiocardiogram, left oblique position, 6 seconds after injection
C Tracing of B.



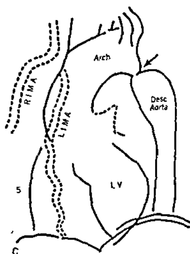


Fig 15 Coarctation of the aorta (arrow), dilatation of aorta proximal and distal to stenosed segment For key to abbreviations, see page 171





Fig 16 Stenosis of left subclavian artery (white arrow), unsuspected unequal dilatation of descending aorta (black arrow)

The various types of dextrocardia can ordinarily be differentiated by conventional roentgen examination, as well as by electrocardiography. Instances of "mirror image" hearts without situs inversus are rare, and the diagnosis should not be accepted unless the superior vena cava and the right auricle are shown by angiocardiography to be on the left side of the cardiac shadow (Fig. 17).

Right-to-Left Intracardiac Shunt. In the presence of a septal defect, a right-to-left shunt ordinarily occurs if there is a lesion



Fig. 17. Dextrocardia, type III. Anatomic arrangement of heart normal, but heart displaced to the right and rotated. Pulmonary artery (white arrow), aorta (black arrows).

raising the pressure in the right auricle or ventricle, or in both. Pulmonary stenosis is the cause in most cases. However, in a few instances, as in the Eisenmenger complex, pulmonary stenosis is not present and there is dilatation of the pulmonary artery. The outstanding clinical manifestation of such intracardiac shunts is cyanosis. Just as the right ventricular blood passes through the septal defect into the general circulation, bypassing the pulmonary vessels, intravenously injected opaque material is seen to travel the same path (Fig 18). In the typical instance of tetralogy of Fallot, that is, in cases which consist of combined interventricular septal defect, dextroposition of the aorta, pulmonary stenosis, and hypertrophy of the right ventricle, the opaque material passes into the right ventricle at about the end of 2 seconds, and the pulmonary artery and aorta are then visualized simultaneously When the amount of shunted blood is high, the aorta and all of its branches are densely outlined within 3 seconds from the end of injection, as compared with the normal period of 5 to 6 seconds. Ordinarily, in these conditions only faint visualization of the left ventricle is obtained, presumably because most of the diodrast is shunted into the aorta, but the degree of pulmonary stenosis and the size of the pulmonary artery are clearly shown This may be of practical importance in the application of recently developed surgical technics for the alleviation of this condition.

Angiocardiography should prove to be valuable in the occasional case where the right ventricular pressure is not greatly elevated and cyanosis is transient. In such a case the sudden injection of 40 cc. of opaque material may elevate the right auricular and ventricular pressures sufficiently to demonstrate the right-to-left shunt, even though it is not present ordinarily Angiocardiography also helps to confirm the diagnosis in those cases of tetralogy of Fallot in which the interventricular septal defect is so large that there is no murmur (cor triloculare)

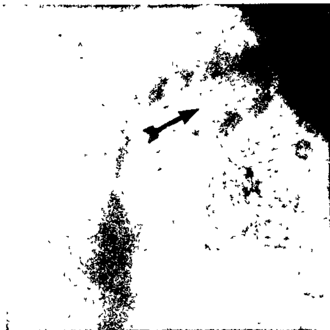
The procedure is invaluable in elucidating the anatomic status in those cases of congenital cyanosis in which the pulmonary artery appears dilated The roentgenologic diagnostic features are: (*1*) simultaneous and rapid visualization of the aorta and the large pulmonary artery, and (*2*) the absence of pulmonary stenosis (Fig 19). In the limited number of cases which we have observed most of the diodrast passed from the right ventricle directly into the two great vessels, only a little passing through the septal defect into the left ventricle

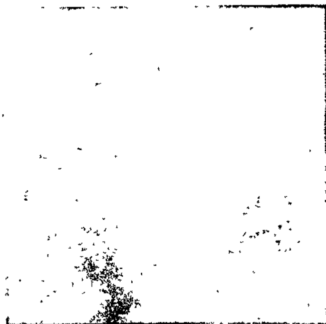
Patent Ductus Arteriosus Practically all cases of this condition which we have studied with the aid of angiocardiography revealed an abnormality in the outline of the aorta, not encountered in normal individuals or in other





Fig 18 Tetralogy of Fallot Angiocardiographic sequence, showing first visualization of right auricle (white arrows), then





simultaneous visualization of aorta and pulmonary artery aorta shows an unexpected irregular deformity and an uneven lumen (arrow)



A: Conventional roentgenogram.
B: Angiocardiogram, left oblique position, 2 seconds after injection.
C: Tracing of B. Black arrows show probable site of interventricular septal defect (black arrows)



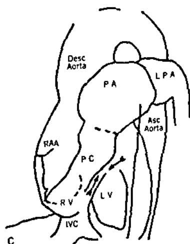


Fig 19 Eisenmenger complex Simultaneous visualization of dilated pulmonary artery and aorta Reflux into inferior vena cava (white arrow) For key to abbreviations, see page 171

cardiac abnormalities, consisting of an apparent localized dilatation of the descending aorta on its anterior aspect just beyond the isthmus.' The changed segment varies in size and shape from a localized bulge to a uniformly dilated segment. This appearance is probably due in most cases to the infundibulum of the ductus, although occasionally it may represent a



Fig 20. Patent ductus arteriosus Infundibulum of ductus (arrow) demonstrated by angiocardiography, metal clips alongside ductus were placed after ligation

traction aneurysm of the aorta caused by the ductus (Fig. 20). The appearance, however, is not pathognomonic Traction on the aorta from any cause will produce the same abnormality

Because in the presence of a patent ductus blood is shunted from the aorta to the pulmonary artery or its left branch, it was anticipated that the ductus itself might be visualized or that there might be prolonged or renewed visualization of the pulmonary arteries. Neither expectation has

been realized; on rare occasions a vascular structure has been seen which might have been the ductus proper, but its position in a maze of other vascular structures prevented identification. Prolonged or renewed visualization of the pulmonary artery was seen in a few cases, but the slight change in the density of this structure was no greater than might be present in any series of roentgenograms and the finding was therefore interpreted with caution. Presumably, clear visualization is impossible because the contrast medium in the pulmonary artery becomes too diluted when it is reshunted through the ductus.

Left-to-Right Intracardiac Shunt. This type of hemodynamic abnormality is the least suitable, in our experience, for angiocardiographic demonstration. The dilution of the diodrast in the left atrium and left ventricle is such that its further dilution when it is shunted from the left ventricle into the right only occasionally results in definite revisualization of the latter

In several cases of interatrial septal defect, the right atrium has seemed to remain visualized after the left became dense, but the demonstration was not unequivocal. In two cases, however, a definite increase in density of the left atrium was noted almost simultaneously with that of the right, and a definite channel was outlined in one of the cases (Figs 21, 22). We presume that in these cases the sudden increase in right atrial pressure, temporarily produced by the rapid intravenous injection, resulted in a reversed interatrial shunt for a few cardiac beats

In interatrial septal defect, a dilated pulmonary artery and dilatation of its major branches usually is found along with a collapsing pulsation, described by Pezzi as a hilar dance; the right ventricle is dilated and the aorta is found to be small (Fig 22, page 136) In some cases, especially in Lutembacher's complex, the left auricle is enlarged.

In isolated interventricular septal defect, the pressure gradient between the two ventricles invariably produces a left-to-right shunt In our experience, the condition is uncommon except in infancy It should be noted in this connection that a clinical differentiation of this condition from subaortic stenosis is difficult Pulse tracings, however, are pathognomonic in the latter condition Attempts to show by means of angiocardiography the shunt or renewed visualization of the right ventricle after it has once emptied have been unsuccessful in all but one case, in which there was unequivocal prolonged diodrast filling of the right ventricle Possibly, cinefluorography may be more successful in demonstrating this defect

Vascular Pattern in the Lungs. Since both inflammatory and neoplastic diseases of the lungs are associated with a disturbance in the



Fig 21 Interatrial septal defect Dilated pulmonary artery (white arrow), persistent visualization of right side of heart when left ventricle (black arrow) already contains diodrast



A: Conventional roentgenogram, postero-anterior view.

B Angiocardiogram, left oblique position, 2 seconds after injection

C Tracing of B

Fig 22 Interatrial septal defect An uncommon instance in which the injection raised the right auricular pressure so that diodrast passed from this chamber to left auricle For key to abbreviations, see page 171

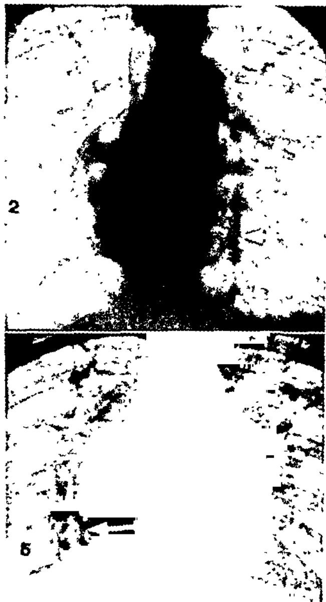


Fig 23. Anomalous pulmonary veins.

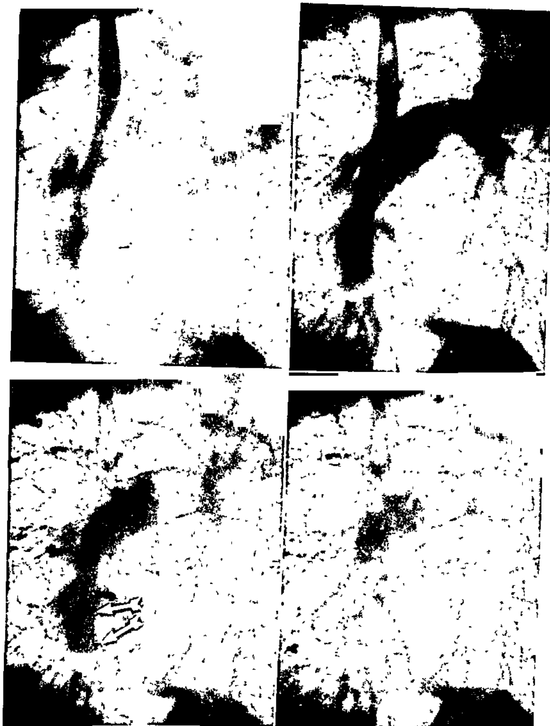
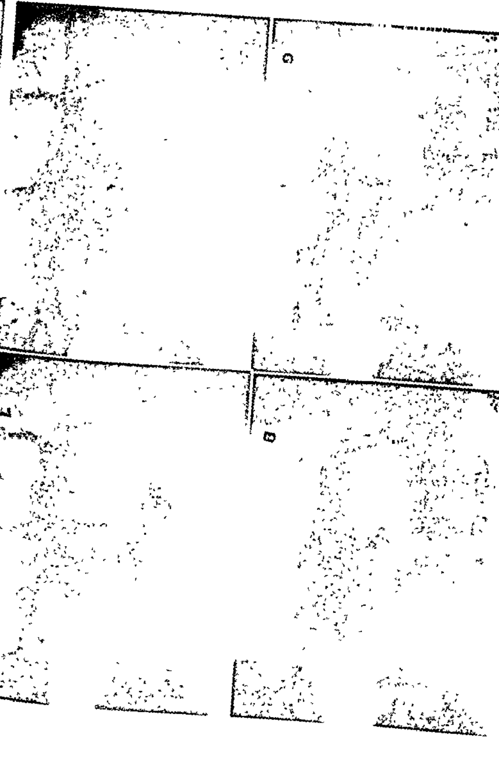


Fig 24 Normal heart, left oblique view Angiocardiographic sequence, apex of right ventricle and right side of interventricular septum (arrows) For key to abbreviations, see page 171.



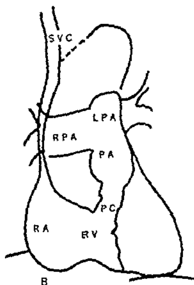
vascular pattern, it might be anticipated that angiocardiography would demonstrate these changes. Robb and Steinberg refer to pressure on and displacement of the hilar vessels by enlarged glands. They observed these changes both in primary and secondary tumors of the mediastinum as well as in tuberculosis. In pulmonary tuberculosis, they describe changes in the pulmonary circulation which fall into three main types These are. diminished vascularity resulting from the narrowing and obliteration of blood vessels in exudative tuberculosis and from fibrosis in the productive type, gross displacement of the intrathoracic cardiovascular structures by extensive pulmonary fibrosis, and displacement and stenosis of the pulmonary artery by tuberculous adenitis. In tuberculous fibrosis, emphysema, chronic pulmonary suppuration, and pulmonary cyst or neoplasm there is a decrease in the vascularity of the involved regions, while in other portions there appears to be an increase in size and number of blood vessels. We have reinvestigated this subject, with confirmatory results. Arterial occlusion in lung cancer is of particular diagnostic value

Roentgenologic Topography of Cardiac Silhouette. *Analysis of the* cardiac topography in various conditions by means of angiocardiography has considerably simplified the teaching of cardiac roentgenology. There is little doubt as to the identity of the individual segments of the cardiac silhouette when serial exposures following injection of diodrast are available (Figs. 24, 25) The advantage of studying *dynamic* material, rather than by injection into the cadaver, as done by Laubry and his associates, is obvious It is perhaps even more important that in place of studying "type cases" and interpolating from them, one can now analyze the configuration in the patient in question.

Angiocardiography, furthermore, has helped to re-evaluate the diagnostic criteria in cardiac roentgenology In the normal heart, for example, it has been shown quite clearly that the conus arteriosus, the upper and anterior angle of the right ventricle from which the pulmonary artery arises, does not reach the left cardiac contour in the postero-anterior view (Fig. 26) The middle left segment consists of the pulmonary artery and its bifurcation Between this structure and the left ventricle lies a portion of the left auricular appendage, the length of which, however, varies greatly, depending upon the habitus of the patient and the angle of inclination of the heart In the long, narrow heart the base of the pulmonary artery may form part of the middle segment, in the transverse heart, only the main stem of the artery appears in the contour with part of the bifurcation In some instances it has been possible to show that the shadow of the descending branch of the left pulmonary artery is apposed to that of the main artery



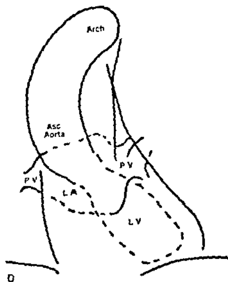
A Angiocardiogram, 2 seconds after injection



B Tracing of A.



C Angiocardiogram, 6 seconds after injection



D Tracing of C

For key to abbreviations, see page 171

Fig 26 Normal heart, postero-anterior view

so that the middle left cardiac segment appears to be convex This can be easily confused with a dilated artery (Figs. 27, 28).

Angiocardiography has made it possible to restudy the position of the interventricular septum, and in particular its direction; it has shown that when the normal right ventricle is opaque, the outline of the septum is convex to the right Angiocardiograms have made it clear also that the first 1.5 to 2.5 inches of the ascending aorta are hidden in the cardiac shadow *and cannot be visualized by any conventional roentgen methods. In the* left oblique and lateral views angiocardiograms have shown the relation of the left atrium to the right ventricle and the pulmonary artery.

A review of the angiocardiograms in cor pulmonale and in mitral disease illustrates the value of this method for studying cardiac topography. We have pointed out in previous publications that in most cases of pulmonary heart disease it is impossible to diagnose right ventricular enlargement on the basis of roentgenograms. We base this conclusion on the fact that prominence of the pulmonary artery segment of the cardiac contour, although considered by Parkinson and Hoyle to be a sign of right ventricular enlargement, more correctly can be considered only an indication of dilatation of this vessel. In other words, while dilatation of the pulmonary artery is frequently associated with right ventricular enlargement, it is actually only an indirect sign of the latter condition (Figs. 29, 30, 31)

In many cases of obstructive emphysema in which clinical evidence suggests right ventricular failure, the transverse diameter of the heart is within normal limits, and fluoroscopic examination in the left oblique position fails to reveal any excessive convexity of the right anterior heart border But in most of these cases angiocardiography reveals a convexity of the interventricular septum to the left, instead of to the right, as found in normal hearts This rearrangement of the inner topography of the cardiac silhouette often leaves unaltered the contour or the size of the heart In other cases, enlargement of the heart to the left is found without any significant widening to the right, the explanation for which may be that the left ventricle has become displaced to the left in response to the altered curve and position of the interventricular septum *Only in advanced cases, frequently* in their terminal stage, has widening of the cardiac silhouette to the right been found, as a result of the presence of right auricular dilatation as part of the failure of the right side of the heart. On the other hand, the role of other cardiac disease in cor pulmonale is well portrayed in angiocardiograms In many instances, where there is an associated hypertension or coronary sclerosis, the left ventricle is dilated and hypertrophied, and the direction of the interventricular septum is not only reversed *back to normal*



Fig 27 Asthenic heart, convexity of segment of pulmonary artery not due to dilatation but to the anatomic position of artery and added projection of left descending pulmonary artery

but the convexity to the right is exaggerated so that the right ventricle is either displaced to the right or is relatively compressed (Fig. 32, page 149) There is little doubt that predominant right heart failure can thus be explained in those cases in which the nature of the disease and the cardiac configuration would lead one to anticipate primary failure of the left ventricle

Angiocardiography has confirmed the presence of dilatation of the pulmonary artery in cor pulmonale, presumably secondary to pulmonary hypertension and sclerosis. With a few exceptions, as, for example, cases of idiopathic pulmonary artery dilatation and some instances of patent ductus arteriosus, it can be assumed that the right ventricle is enlarged when the pulmonary artery is definitely dilated A possible further exception, now under investigation, is the apparent dilatation of this vessel which sometimes occurs in Graves' disease.



Fig 28A–C Dilated pulmonary artery associated with traction by tuberculous nodes


B
C





Fig 29 Lues of aorta and pulmonary artery Only by angiocardiography could the degree of dilatation be estimated

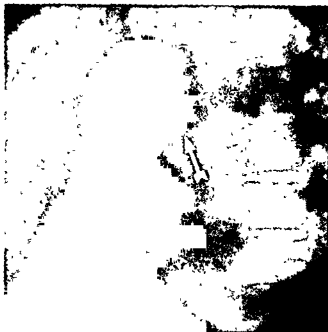
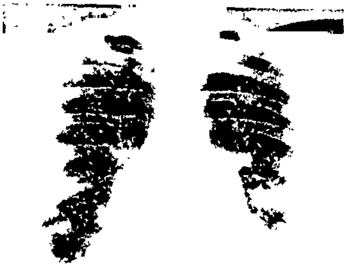




Fig 30 Markedly dilated pulmonary artery (white arrow); aorta irregularly dilated and of uneven lumen (black arrow).



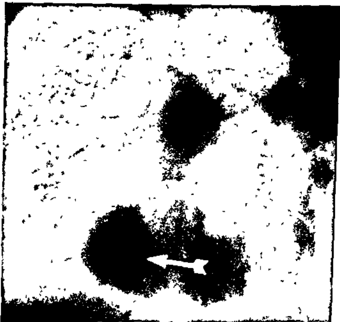


Fig 31 Cor pulmonale Pulmonary artery markedly dilated, right ventricle dilated, interventricular septum directed convexly to the left.

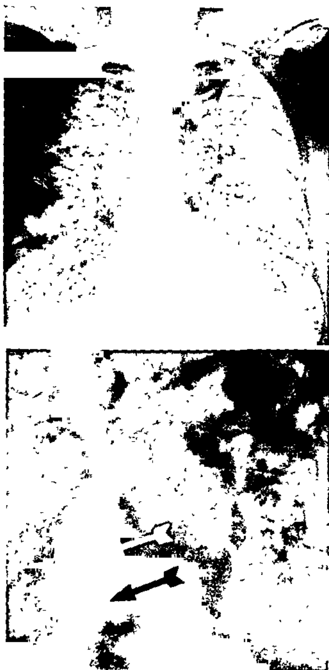
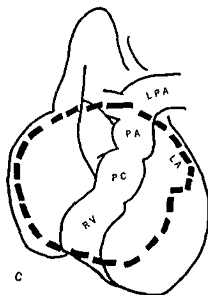


Fig 32 Cor pulmonale Pulmonary artery only slightly dilated, right ventricle enlarged, straight interventricular septum as result of compensation by hypertrophied and dilated left ventricle due to hypertension





A Angiocardiogram, 2 seconds after injection
B Angiocardiogram, 10 seconds after injection
C, Tracing of A combined with B, broken line outlines left auricle

Fig 33 Mitral configuration, postero-anterior view, showing predominant role played by enlarged left auricle, pulmonary conus and artery are completely hidden in the cardiac shadow For key to abbreviations, see page 171

In the mitral configuration, the middle left cardiac segment has often been misinterpreted. Many authors have considered that elongation and exaggerated convexity of this segment is due to the lengthened outflow tract of the right ventricle. Angiocardiographic analysis, however, has shown that the large left atrium is the dominating factor, this chamber actually constituting a major portion of the middle left segment in most cases (Fig. 33). Furthermore, the right ventricle is bowed anteriorly, while the pulmonary artery is displaced cephalad. Both are elongated and both are bowed to conform to the large left atrium. In the cases we have studied, the pulmonary artery was not found to be significantly dilated, which incidentally is also the common pathologic experience in mitral disease. The left oblique view has shown that enlargement of the heart to the right and anteriorly is primarily due to the dilated left atrium; in many cases it constitutes the bulk of the heart, with the right ventricle often appearing like an appendage to this chamber.

These data provide convincing evidence that in the mitral configuration the convexity and elongation of the middle left segment are not a direct indication of right ventricular dilatation, although hypertrophy and dilatation of this chamber are regularly found when the left atrium is significantly dilated. One cannot, therefore, determine the degree of ventricular enlargement from this indirect evidence. It is also apparent that the degree of cardiac enlargement to the right and anteriorly, as conventionally determined in the left oblique view, is not based upon direct visualization of the contour of the right chambers. Occasionally, the left atrium is so dense that its shadow can be subtracted from the whole and the size of the remainder may then be attributed to the right auricle and ventricle. It follows that the common concept of a demonstrable right ventricular dilatation early in mitral disease is unproved, at least as far as roentgenologic evidence is concerned, and it must further be pointed out that in prognosis such data are not useful unless they are employed critically and in association with clinical evidence.

Physiologic Applications of Angiocardiography

Cardiac Chambers. The possibility of accurate physiologic studies of the heart by angiocardiography has been partially explored, both in animals and in man. Westermark, for example, using simultaneous roentgenocinematography and electrocardiography has shown experimentally that the circulation time through the lesser circulation is 1.4 to 2.5 seconds, with an average of 1.7 seconds. His studies indicated that the auriculoventricular valves open at the P wave and close immediately before

the Q wave. It is only during this period that the ventricle seems to fill up with blood, while the auricle only partially empties itself, apparently thus forming a constant blood reservoir. The auricle always fills rapidly immediately after the T wave, at the beginning of diastole.

Westermark found that the systolic contraction of the ventricle begins in conjunction with the QRS complex, with a downward movement of the auriculoventricular junction, which makes it appear to bulge like a cone into the ventricle. The downward movement of the atrioventricular junction is probably caused by a contraction of the interventricular septum; the ventricular wall then begins to contract at the apex while the atrioventricular junction returns to its former position. This occurs between the S and T waves, and during this period the space between the auriculoventricular junction and the inner contour of the ventricular apex seems to remain unaltered. The ventricular wall then continues its contraction successively up to the conus arteriosus. The semilunar valves apparently do not open until the beginning of the T wave, when the contraction wave through the ventricular wall has reached the conus and the ventricular pressure has reached its maximum The ventricle has then almost completely emptied itself, and supposedly remains in prolonged contraction and retains a small residue At the P wave, the ventricle relaxes and the atrioventricular valves open.

On the other hand, studies by Benner, Kjellberg, and Sjostrand indicate that although angiocardiography records changes in volume during contraction of the auricles and ventricles, opening and closing of the valves cannot be determined accurately by this method because a certain concentration of the contrast medium is necessary before it can be detected Further studies suggested that the rest volume in the ventricles during systole is larger than has been assumed from animal experiments Study of this subject in man, particularly with alterations in hemodynamics such as caused by drugs, exercise, and disease should prove important

Our experience with cinefluorography following intravenous injection of diodrast in man is still very limited, and the results have not been subjected to precise analysis We found, as did Westermark in animals, that the attachment ring of the atrioventricular valves moves toward the ventricular apex during systole, and that this movement elongates the atrium It is possible that a negative intra-atrial pressure is thus produced, and that this in turn may be an important factor in atrial filling

Little is known about the function of the conus arteriosus (the outflow segment of the right ventricle) Fluoroscopy has shown that calcified aortic valves and probably also the pulmonic valve change their level with

the phase of the cardiac cycle, and this has been thought to be due to contraction of the ventricular muscle Our angiocardiographic data, however, suggest that the hemodynamic function of the conus may be a more complicated one. It has been frequently observed that during the isometric contraction and early ejection phase this segment balloons out, perhaps thus building up pressure for the opening of the semilunar valves and for a maximal release of energy as the valves open. We wish to emphasize that these are merely preliminary observations which will have to be corroborated by systematic study.



Fig 34 Kymogram of interventricular septal movements during angiocardiography, arrows indicate pulmonary artery

During the angiocardiographic investigation of the circulation in pulmonary heart disease, our attention was attracted to the position and movements of the interventricular septum, a study of which in man can be made only by angiocardiography Investigations were carried out by multiple exposures, cinefluorography, and roentgenokymography during the passage of diodrast through the heart (Fig 34) The change in the direction of the

the Q wave. It is only during this period that the ventricle seems to fill up with blood, while the auricle only partially empties itself, apparently thus forming a constant blood reservoir. The auricle always fills rapidly immediately after the T wave, at the beginning of diastole

Westermark found that the systolic contraction of the ventricle begins in conjunction with the QRS complex, with a downward movement of the auriculoventricular junction, which makes it appear to bulge like a cone into the ventricle. The downward movement of the atrioventricular junction is probably caused by a contraction of the interventricular septum; the ventricular wall then begins to contract at the apex while the atrioventricular junction returns to its former position. This occurs between the S and T waves, and during this period the space between the auriculoventricular junction and the inner contour of the ventricular apex seems to remain unaltered. The ventricular wall then continues its contraction successively up to the conus arteriosus. The semilunar valves apparently do not open until the beginning of the T wave, when the contraction wave through the ventricular wall has reached the conus and the ventricular pressure has reached its maximum The ventricle has then almost completely emptied itself, and supposedly remains in prolonged contraction and retains a small residue. At the P wave, the ventricle relaxes and the atrioventricular valves open

On the other hand, studies by Benner, Kjellberg, and Sjostrand indicate that although angiocardiography records changes in volume during contraction of the auricles and ventricles, opening and closing of the valves cannot be determined accurately by this method because a certain concentration of the contrast medium is necessary before it can be detected Further studies suggested that the rest volume in the ventricles during systole is larger than has been assumed from animal experiments Study of this subject in man, particularly with alterations in hemodynamics such as caused by drugs, exercise, and disease should prove important

Our experience with cinefluorography following intravenous injection of diodrast in man is still very limited, and the results have not been subjected to precise analysis We found, as did Westermark in animals, that the attachment ring of the atrioventricular valves moves toward the ventricular apex during systole, and that this movement elongates the atrium It is possible that a negative intra-atrial pressure is thus produced, and that this in turn may be an important factor in atrial filling

Little is known about the function of the conus arteriosus (the outflow segment of the right ventricle) Fluoroscopy has shown that calcified aortic valves and probably also the pulmonic valve change their level with

right atrium and the large veins leading to it act as a functional unit, and that temporary storage of blood in the large veins permits the right atrium to accommodate or "digest" a large venous return.

The Great Vessels. Angiocardiography, as a rule, demonstrates clearly the superior vena cava, the pulmonary artery, and the aorta. Peristalsis-like contractions of the large veins have been noted, and the systolic and diastolic size of the pulmonary artery and aorta can be measured. In fact, angiocardiography is the method of choice for this determination, *since these vessels cannot be outlined during life by any other* method. The cyclic variations in diameter can be determined by kymography or by exposures in predetermined phases of diastole and systole. At present, the precise determination of size is of little value in clinical medicine, although accurate information is required when stroke output is evaluated by physical methods or when the ballistocardiograph is used. Whether angiocardiography is necessary in all cases when these methods are employed is as yet uncertain. Preliminary studies indicate that in the normal individual, at least, the diameter of the aortic isthmus is in proportion to the vessel diameter at most of the other levels of the aorta. Statistical analysis may therefore prove that the measurement of the aortic isthmus as determined by the simple Kreuzfuchs' method is all that is necessary. Studies are also under way to determine the diameter of the pulmonary artery in Graves' disease and whether it is an indication of the tension in this vessel. When combined with data regarding right intra-auricular and intraventricular pressures obtained by Cournand's method, considerable information regarding the right side of the heart in this disease is anticipated (Fig. 36).

Size of Cardiac Chambers and Musculature. Preliminary studies indicate that although angiocardiography provides information on the approximate size of the cardiac chambers in man, it is unlikely that precise values will be obtained, for a number of reasons. In the usual procedure, 35 to 50 cc. of the contrast substance are introduced into an antecubital vein in about 1.5 seconds. However, although attempts have been made to control the pressure and speed of the injection, no way has yet been found to prevent retrograde leakage into collateral veins about the shoulders and neck. Furthermore, venous valves often impede the injection unpredictably, and, in addition, the degree of dilution of the opaque substance varies from case to case. It has already been pointed out (page 154) that the right auricle may compensate for sudden distention by a reflux of the contrast substance into the inferior vena cava and hepatic veins, but there is no way of determining the degree of this reflux. Direct injection into the

interventricular septum as the size of the right ventricle increases has been mentioned (page 142). Preliminary analysis of the movements of the septum suggest that it normally moves with the left ventricle, moving to the left with systole. However, with dilatation of the right ventricle, the septum appears to participate more actively with contraction of that ventricle, moving to the right with systole. It is likely that under these conditions both position and movement are more related to right apical hypertrophy and dilatation than to the difference in pressure between the two ventricles.



Fig 35 Isolated interventricular septal defect, reflux into inferior vena cava and hepatic veins.

Another of our observations is of considerable physiologic interest. In several of our cases—particularly in children, asthenic individuals, and some cases of congenital cardiac disease—a reflux of diodrast into the inferior vena cava, hepatic veins, and innominate veins has occurred, presumably due to the rapid overloading of the right atrium or ventricle by the injection. Venous pulse tracings made during the injection showed no evidence of systolic auricular filling and only a suggestive increase of all wave amplitudes, while motion pictures revealed that the reflux occurred in presystole or during atrial contraction. It seems likely then that the

of size, although the dilution of the contrast medium may interfere. The thickness of the muscle at the left ventricular apex can be measured in diastole in those cases in which there is a sufficient concentration of the contrast substance, while comparison of the roentgenograms visualizing right and left ventricles permits an approximate evaluation of the thickness of the interventricular septum.

Arteriography

Peripheral Arteriography. The most recent review of this method is that presented by Camp and Allen. They point out that in the interpretation of roentgenograms of peripheral arteries, one is chiefly concerned with: (*1*) congenital variations from the usual formation of the vascular system; (*2*) alterations in the lumens of the arteries, consisting of irregularities in contour, diminution in caliber, and complete occlusion; (*3*) the presence or absence of collateral circulation, and its situation and extent. Care must be used in the interpretation of the roentgenograms, since changes resulting from errors in technic of injection or in timing of the exposure may erroneously be taken as evidence of organic disease



Fig 37 Arteriogram of normal arteries

Normal Arteriogram This is characterized by (*1*) a smooth and uninterrupted contour of the lumens of the injected arteries, (*2*) a direct course of these vessels, and (*3*) the presence of no more than a minimum of collateral circulation (Fig 37) Spasm of a portion of an artery is characterized by smooth diminution in caliber to a point of complete or almost complete obliteration and an equally smooth increase in size up to normal It does not appear consistently.

right auricle through an intravenous catheter has been unsuccessful in our hands; we found that the small caliber of the catheter limits the speed of injection. In animal experiments this has been overcome by the use of *amounts of thorotrast impossible to use in man. There is, furthermore,* some evidence that interauricular injection of diodrast is not without danger, although in the authors' limited experience there have been no untoward results.



Fig 36 Intubation of right auricle for measurement of intra-atrial pressures

*By using a multiple exposure technic, the right ventricle can almost al*ways be demonstrated unobscured by the shadow of the right auricle It seems probable that simultaneous exposure made in two directions at right angles to each other would permit a fairly accurate determination of the size of the ventricle The speed of the injection would probably not alter this determination significantly, but exposures would have to be made in predetermined phases of the cardiac cycle

The left auricle has not been consistently vizualized, so far. *Exposure* in predetermined phases of the cardiac cycle will probably result in sharper outlines of the left ventricle, thus permitting a reasonably accurate analysis

We have succeeded in demonstrating the presence of a subclavian arteriovenous fistula by using either of two methods. The first method consists of injecting an antecubital vein on the involved side, visualizing the subclavian vein, watching it empty while the contrast material passed through the heart and aorta, visualizing the subclavian artery, and almost simultaneously, the vein. The second method consists of injecting an antecubital

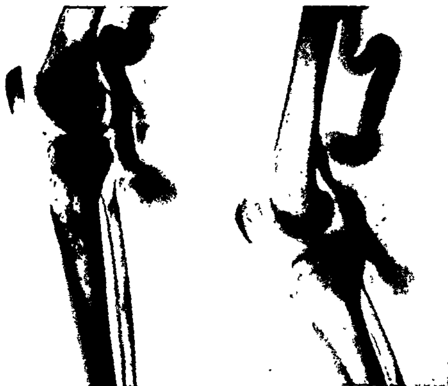


Fig 38 Visualization of arteriovenous fistula following injection of femoral artery

vein on the uninvolved side and visualizing the involved subclavian artery, followed immediately by visualization of the vein

Raynaud's Disease Allen and Barker describe an absence of filling of the distal parts of the digital arteries and their diminished caliber.

Cerebral Arteriography. This procedure is used (*1*) to determine abnormalities in the size, lumen, and course of the cerebral arteries; (*2*) to show by changes in the position, course, size, competency, and character of the cerebral vessels the presence of a space-occupying lesion, (*3*) to

Thrombo-Angiitis Obliterans. The following is summarized from Camp and Allen:

Roentgenologically, this disease does not have a uniform appearance. Arteries of normal appearance may be seen in close proximity to those extensively involved Nor does the disease show uniformity of progress in one direction, either proximally or distally One segment of an artery may be involved in a process varying from slight to extensive, while other segments may appear normal. This patchy distribution of the disease is characteristic. In the upper extremity, the digital and palmar arteries are the ones most frequently involved. The three stages of the disease are: (*1*) Irregularity in contour and in the size of the lumen, the filling defects are likely to be rounded (*2*) Shaggy and moth-eaten outline; lumen reduced in size; irregular and rapidly changing course; the channel may be divided. (*3*) Complete occlusion, not abrupt but rounded, with its convexity toward the occluded portion.

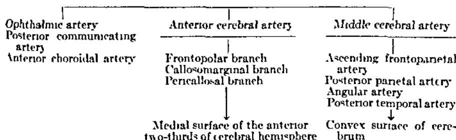
Collateral Circulation. This term is used to describe arteries and evidence of circulation in arteries which ordinarily are seen only in the presence of arterial disease According to Camp and Allen, collateral circulation may be caused by. (*1*) Anastomosis, in which a large branch artery arises above the point of occlusion, runs parallel to the diseased artery, and joins the parent artery distal to the occlusion In thrombo-angiitis anastomosis of two main arteries occurs only infrequently. (*2*) Lateral branching, in which a healthy artery sends out numerous branches laterally to a diseased companion artery. (*3*) Prolongation of proximal branches to join with peripheral collateral arteries. (*4*) Terminal branching from a point proximal to the occlusion (*5*) A network of collateral arteries, the origin, direction, and termination of which may be entirely obscured in the irregular network These authors produce evidence that a great many existing arteries are not shown on arteriograms because they are not in an actively functioning state This is probably due to vasomotor control, responding to the circulatory needs of the extremity

Arteriosclerosis Quoting Camp and Allen again, in this condition the vessels are characterized by extremely irregular lumens, reduction in caliber and a moth-eaten appearance The degree of collateral circulation varies. The most important use for arteriography in arteriosclerosis is the determination of the optimum level for amputation.

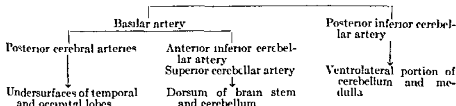
Aneurysm This condition is diagnosed roentgenologically by the presence of fusiform or saccular dilatation of the vessel involved

Arteriovenous Fistula In this disease the arteriogram will show (*1*) dilatation of the arteries leading to the fistula, (*2*) absence of normal filling of the arteries distal to the fistula, (*3*) pooling of the opaque medium in the region of the fistula, and (*4*) simultaneous visualization of the vein (Fig. 38)

A INTERNAL CAROTID ARTERY

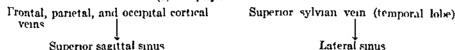


B VERTEBRAL ARTERIAL SYSTEM

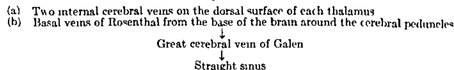


C INTRACRANIAL VENOUS CHANNELS

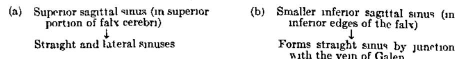
(1) Superficial cerebral veins



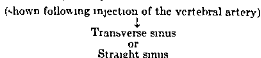
(2) Deep cerebral veins



(3) Venous sinuses



(4) Superior cerebellar veins



demonstrate the nature and the size of certain angiomatous malformations of the cerebral vessels.

Cerebral angiography is usually limited to the study of supratentorial lesions, the results having been found more satisfactory than for lesions in the posterior fossa. A method of visualizing the vertebral system has already been described (page 109).

Normal Arterial System. The main cerebral branches and their areas of supply, as given by List *et al.*, and Wakely and Orley, are given here in schematic form (Figs. 39 to 42).

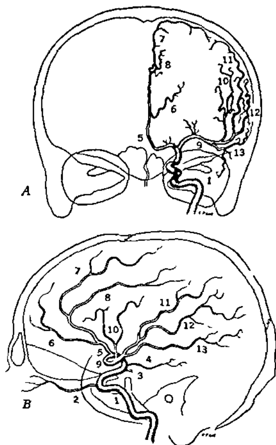


Fig 39 Schematic drawing of normal internal carotid artery A, anteroposterior projection, B, lateral projection (From List, Burge, and Hodges)
1 Internal carotid artery 2 Ophthalmic artery 3 Posterior communicating artery 4 Anterior choroidal artery 5 Anterior cerebral artery 6 Frontopolar artery. 7 Callosomarginal artery 8 Pericallosal artery 9 Middle cerebral artery 10 Ascending frontoparietal artery 11 Posterior parietal artery. 12 Angular artery. 13 Posterior temporal artery.

Contraindications to cerebral arteriography are marked hypertension, advanced arteriosclerosis, acute intracerebral or subarachnoid hemorrhage, recent thrombosis or embolism of cerebral vessels. For the use of cerebral arteriography in the localization of cerebral tumors we have drawn freely on the *Textbook of Neuro-Radiology*, by Wakely and Orley.



Fig 42 Arteriogram of normal internal carotid artery

Frontal Tumors Generally speaking, the carotid siphon is displaced downward The anterior cerebral artery is frequently compressed, or considerably displaced backward, downward, and laterad The position of the internal carotid artery contiguous to the sella may be displaced downward and backward

Posterior and Anterior Parietal Tumors The frontal branches of the anterior cerebral artery are displaced forward, and the part of the pericallosal artery which is situated behind the genu is displaced downward, so that, in comparison with the normal side, the sylvian group lies closer to the pericallosal artery The anterior cerebral artery and the middle and posterior part of the pericallosal artery are displaced laterally toward the healthy side

Parietal Lobe Tumors The vessels of this portion of the brain are depressed, but the anteroposterior view is not likely to show lateral displace-

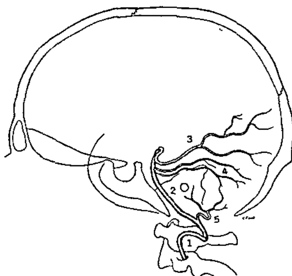


Fig 40 Schematic drawing of a normal vertebral arteriogram in lateral projection 1 Vertebral artery 2 Basilar artery 3 Posterior cerebral artery 4 Superior cerebellar artery 5 Posterior inferior cerebellar artery

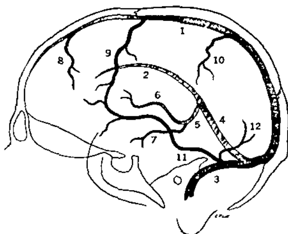


Fig 41 Schematic drawing of a normal venogram in lateral projection, obtained by carotid injection Superficial veins are more darkly shaded than the sinuses and deep veins

1 Superior sagittal sinus 2 Inferior sagittal sinus 3 Transverse sinus 4 Straight sinus 5 Great cerebral vein of Galen 6 Internal cerebral vein 7 Basal vein of Rosenthal 8 Frontal ascending vein 9 Rolandic vein of Trolard 10 Parietal ascending vein 11 Communicating temporal vein of Labbé 12 Descending tempero-occipital vein

Arteriography of Bone Tumors. Fariñas described this procedure in 1937. He states that in benign tumors the vessels are displaced, but are regular in caliber and not increased in number. Giant cell tumors do not show an intratumoral circulation, but an artery encircling the capsule can be seen. Malignant tumors reveal numerous vascular pedicles and an irregular network of newly formed vessels, all of the same caliber. In osteomyelitis, the number and caliber of the vessels are smaller than normal.

Venography

Venography may be performed directly, or indirectly following intra-arterial injection. The advantage of the latter is that most of the functioning veins of an extremity are visualized at one time. Its disadvantages are dilution of the contrast material and the difficulty of correctly timing the x-ray exposure. With direct venography, the better definition is counterbalanced by the fact that when tourniquets are not used the medium will proceed along the path which is most direct and offers the least resistance. As a result, only certain veins may be visualized. Furthermore, interpretation is sometimes difficult because of venospasm, or because of the occasional obstruction of venous valves.

Upper Extremity. The median basilic and axillary veins are visualized by the slow injection of a 35 per cent diodrast solution. The subclavian vein is seen as far as the lower margin of the clavicle, at which point it narrows. Visualization of the subclavian vein beyond this point was reviewed on page 111. Retrograde visualization of the tributaries is variable and usually is possible for a short distance only. Moderate saccular dilatations are seen at the sites of valves. Obstruction is indicated by dilatation proximal to the site of obstruction and lack of visualization of the vein beyond it, by increased dilatation at the valve sites, and by visualization of many diverging and tortuous collateral veins. In complete obstruction, a filling defect corresponding to a thrombus may appear in the vein.

Normal Venogram of the Lower Extremity. The following vessels (Fig. 44) are to be seen.

Femoral Vein. A thick cord ascending in a slightly mesial direction from the knee joint and crossing the outline of the femur. Valves may sometimes be seen in it. In the femoral triangle it is joined by the deep femoral vein and then by the large saphenous vein, after which it passes into the pelvis to form the iliac vein. This in turn joins with that of the opposite side to form the inferior vena cava. In the normal venogram the femoral vein is visualized regularly.

ment of the anterior cerebral artery. When the tumor is deep in the brain, the contiguous vessels may be stretched over the lesion and separated from each other.

Temporal Lobe Tumors Anteriorly located tumors may displace the distal part of the carotid siphon downward to such an extent that it comes to lie quite close to the lesser wing of the sphenoid bone. The middle cerebral artery is raised and displaced forward. In the anteroposterior view, large tumors produce a slight curvature of the anterior cerebral artery, and the middle cerebral artery is displaced upward

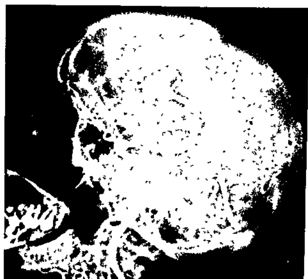


Fig 43 Arteriogram of internal carotid artery, showing vascular malformation

Posteriorly located tumors, according to Cairns and Jupe, elevate the posterior middle cerebral vessels, leaving the carotid artery unaffected

Occipital Tumors The middle cerebral vessels are displaced mainly forward and upward

Tumors of the Middle Fossa Both anterior cerebral arteries may be filled The anterior cerebral artery on the affected side may be displaced into the opposite half of the skull, but the middle cerebral artery is generally not affected

Cerebral Aneurysms These are revealed by a rounded mass of opaque medium communicating with or replacing a contiguous vessel A clot may produce a filling defect in the aneurysm, so that it appears smaller than it actually is Arteriovenous fistula is characterized by large, dilated, tortuous vessels communicating with a mass of smaller, dilated, coiled vessels Venous angiomas are difficult to demonstrate (Fig 43).

The former is the wider of the two; it passes downward and mesially toward the inner malleolus. The latter passes laterally, crossing the shadow of the anterior tibial artery.

Although in general the course of the veins corresponds to that of the arteries, there are many variations. The main venous trunk may be double or single, thick or thin. The veins may or may not loosely follow the arteries throughout their course. Furthermore, the deep veins are partially obscured by the superficial veins. The anterior tibial vein, therefore, is usually to be seen in the space between tibia and fibula, although it sometimes may overlap the outer edge of the tibia. The posterior tibial vein, which is almost always a double vein, stands out against the background of the tibia, over which it passes laterally toward the popliteal vein. The peroneal vein is not so consistently visualized; when it is seen, it follows approximately the course of the artery. Occasionally, double sural veins are seen mesially and laterally, following the course of the sural arteries. Ordinarily, they are not seen in the normal venogram, and their presence, while not definitely indicative of an abnormality, calls for additional study. The superficial cutaneous veins are also not seen ordinarily. When seen, they appear as slender shadows with even lumens, running longitudinally or anastomosing with the deep venous system.

In the normal venogram one expects to see the proximal portions [illegible] deep veins of the calf, as well as the poplit[illegible] nosis of ven[illegible] of those ve[illegible] the presence of a filling defect in a [illegible] is partially obstructed, and (3) the visualization of anastomotic channels ordinarily not outlined (Figs. 45 to 47).

Venous Thrombosis and Pulmonary Embolism. In the last decade venography of the lower extremity has been used chiefly to demonstrate thrombophlebitis, or "phlebothrombosis," a term used by some authors who wish to emphasize the bland nature of the local disease. There seems to be no doubt that, with the exception of cardiac thrombosis, the primary source of pulmonary embolism is venous thrombosis in the calf propagated cephalad, whether the condition occurs postoperatively or otherwise. While interruption of the femoral vein and, if necessary, removal of thrombi in the femoral and iliac veins, or even in the vena cava, do not cure the morbid pulmonary process already started, they do prevent further injury. Furthermore, even a first attack may be avoided by careful postoperative watch over temperature, pulse, and respiration, as well as by examination of the legs. The experience in The Mount Sinai Hospital (Neuhof and Sareson) leads to the same conclusion as that expressed by Allen, Linton,

Popliteal Vein. This vein is of less uniform structure than the femoral, and presents many more anatomic variations. Its length depends upon whether the junction of tibial veins is at a high or low level. In many cases the vein is double, and sometimes it shows a large, bulbous thickening.



Fig. 44. Venogram of normal lower extremity.

Deep Veins of the Lower Leg. These veins, often paired, accompany the three great arterial trunks, for which reason the latter are described here. The first large branch of the popliteal artery is the anterior tibial artery. It starts laterally, then bends downward and mesially until it reaches the mid-line of the leg. For the greater part of its course it appears on the venogram in the space between tibia and fibula. A few centimeters below the origin of the anterior tibial artery the popliteal artery divides at an acute angle into two narrower arteries, the posterior tibial and the peroneal.

and Donaldson, namely, that venography is of only limited value in this condition. In fact, there are two reasons why venography is now performed only rarely for suspected thrombosis of a calf vein. In the majority of cases the indications for femoral vein surgery are provided by clinical examination, and venography cannot materially influence the decision to operate. Another reason is that venography of the calf does not necessarily depict the presence or absence of thrombi. Allen, Linton, and Donaldson state that they obtained a negative venogram in one-third of a series of cases with positive clinical evidence of thrombosis, while we ourselves have observed, with Neuhof and Sareson, a key case which yielded a typically positive venogram, but which at autopsy revealed veins free of thrombi (Fig. 48).

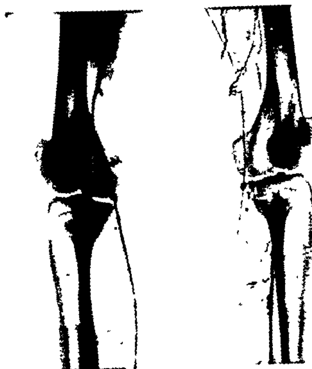


Fig. 48. A case of apparent occlusion of veins of calf; on autopsy, however, they were found patent.

Opposite Fig. 45. Venogram of lower extremity: thrombosis of veins of calf.
Fig. 46. Thrombosis of veins of calf and femoral vein, filling defect in femoral vein (arrow).
Fig. 47. Thrombosis of femoral vein, retrograde filling of femoral vein down to thrombus.



Fig. 45



Fig. 47



Fig. 46A



Fig. 46B

We still occasionally resort to visualization of the femoral vein, since in our experience the venographic evidence of thrombosis of this vein is reliable. The procedure is particularly useful in those cases in which the clinical evidence is inconclusive as to the side to be operated on. Even in such cases, however, there is a growing tendency to make the decision on clinical evidence alone.

Varicose Veins of the Lower Extremity. A description of the technic for this study may be found in Barber and Orley. Stereoscopic roentgenograms are essential for the investigation The tube and cassette are centered in relation to the part to be examined One exposure is made at the end of an injection of 10 cc. of abrodil, the second at the end of a second injection of a like amount, the tube having been moved through the stereoscopic shift. When a normal superficial vein is injected, there is no flow into the deep venous system; the opaque fluid ascends the internal saphenous vein, backflow being stopped by the nearest valve below the point of injection, but in the presence of varicose veins, the contrast medium may enter the deep system through anastomotic channels at the level of the ankle and the knee joint (but not through the venae comites). Large ampullar dilatations of the internal saphenous veins are frequently seen at the level of the medial condyle of the tibia. The flow of the medium is both forward and backward, the retrograde flow being due to the incompetency of the valve (Fig 49)

KEY TO ABBREVIATIONS ON TRACINGS

ASC, Ascending
IVC, Inferior vena cava
LA, Left auricle
LIMA, Left internal mammary artery
RIMA, Right internal mammary artery
LPA, Left pulmonary artery
PA, Pulmonary artery
PC, Pulmonary conus
RA, Right auricle
RAA, Right auricular appendage
SD, Septal defect
SVC, Superior vena cava



Fig 49 Arteriogram and venogram of diffuse congenital phlebectasia

The Surgical Treatment of Hypertension

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Introduction

Hypertension confronts the physician with a difficult problem in diagnosis and therapy. It may be recognized early, and associated with a labile blood pressure and little evidence of cardiac, cerebral, or renal vascular disease. It may be observed and treated late, and after blood vessels of the brain, heart, or kidney have been seriously damaged. Careful study may reveal a plausible explanation of the origin of the hypertension as a renal disease, an endocrine disorder, a toxemia of pregnancy, a coarctation of the aorta, or an adrenal or brain tumor. Often examination fails to determine the etiology and reveals only evidence of secondary cardiovascular or renal damage. Usually the disease is chronic and slowly progressive, responding only partially or temporarily to the conventional treatment of rest, reassurance, and sedation or to other forms of medicinal or dietary therapy. Occasionally it is acute, temporarily during an episode of hypertensive encephalopathy, or permanently during a malignant terminal stage.

The introduction of surgery of the sympathetic nervous system as a treatment of hypertension has increased the physician's responsibility. Critical evaluation by cardiovascular and surgical clinics has established sympathectomy as a valuable adjunct to medical management in certain cases. The physician must decide for each patient whether his particular early or late, acute or chronic disease process warrants a surgical consultation or a sympathectomy. He must balance the disability and the danger to life of the disease against the operation with its temporary discomfort and disability and its therapeutic limitations. The following presentation of certain clinical and physiologic observations may aid this decision.

Sympathectomies Performed for Hypertension

The early development of the surgical treatment of hypertension, from the theoretic suggestions of Daniélopolu, Bruening, Kraus, and Pende through the early surgical efforts of Piere, Rossi, and others to the first operation in this country by Adson in 1930 has been reviewed by Adson,

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Craig, and Brown (1), Heuer (2), Martin (3), and others. A review of later developments (4) will here be summarized and brought up to date in order to present the evolution of the technic of sympathectomy The recent lumbodorsal splanchnicectomy and the subtotal to total paravertebral sympathectomy, splanchnicectomy and celiac ganglionectomy are particu-

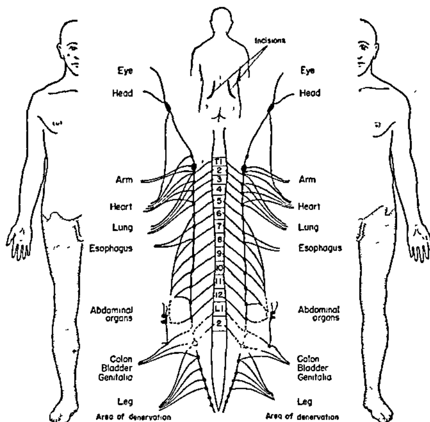


Fig 1 Subdiaphragmatic splanchnicectomy — Adson

larly emphasized Published reports of the effectiveness of operations for hypertension, interpreted as accurately as possible, have been grouped together in Table I

Bilateral Section of Anterior Spinal Nerve Roots from the Sixth Thoracic to the Second Lumbar Inclusive This operation was first performed in 1930 by Adson Later, Adson *et al* (1,5) reported good results in 13 of a

TABLE I

SUMMARY OF OPERATIONS IN 950 CASES OF HYPERTENSION

Source	Operation	Number of patients	Wagener-Keith classification				Observation, months		No of deaths		Effect on blood pressure			Improvement, %	
			I	II	III	IV	Min	Max	During period of obs	Operative	Little or none	Significant	Normal, or below 150/100	Objective	Symptomatic
Allen and Adson (10)	Subdiaphragmatic splanchnicectomy	224	11	137	69	7	6 →	60	34	1	156	52	16		94
Peet, Woods, and Braden (14)	Supradiaphragmatic splanchnicectomy	350	15	77	147	94	9 →	84	95	12	141	93	56	45+	86
Rytand and Holman (22)	Supradiaphragmatic splanchnicectomy	40					1 →	48	11	8	26	5	1	30+	30
Heuer and Glenn (8)	Rhizotomy	23					54 →	78	14	2	6	12	1		94
	Supradiaphragmatic splanchnicectomy	12					36 →	68	6	0	5	6	1		50
	Subdiaphragmatic splanchnicectomy	22					2 →	43	6	3	8	10	0	Little	77
Bartels, Poppen, and Richards (12)	Supradiaphragmatic splanchnicectomy	13					72 →	120	9	0	13	0	0	.	.
	Sub- or transdiaphragmatic splanchnicectomy, and often nephro-omentopexy	41	0	35	6	0	8 →	66	1	2	15	15	9	..	74
Ayman and Goldshine (23)	Supra- and subdiaphragmatic splanchnicectomy	14	0	4	6	3	7 →	63	4	1	7	4	2	38+	91
Smithwick (25)	Lumbodorsal splanchnicectomy	156	45	43	41	18	12 →	60	.	4	32	124		63+	.
Grimson	Lumbodorsal splanchnicectomy	14	2	5	4	2	18 →	54	4	1	8	4	1	46	40
	Paravertebral sympathectomy	41	4	18	7	9	18 →	76	7	3	9	20	0	76	79

onectomy Peet devised the operation illustrated in Figure 2 in 1933 and has since employed it on more than 900 patients. Peet, Woods, and Braden (14) review the effect of the operation in 350 consecutive patients (Table I), and Woods and Peet (15) compared the delayed mortality among 76 cases observed 5 to 7 years after operation with the mortality during medical

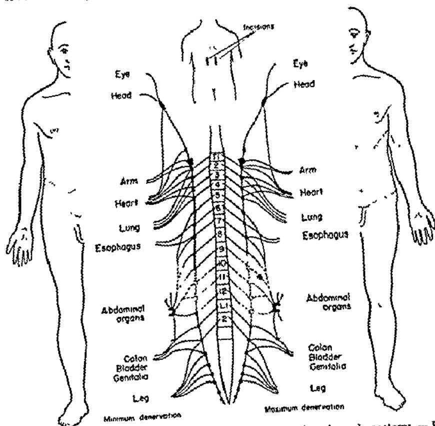


Fig 2 Supradiaphragmatic splanchnicectomy and lower dorsal ganglionectomy — Peet

treatment of 219 patients reported by Wagener and Keith (16) The survival rate of patients of Wagener-Keith groups I, III, and IV treated surgically seemed to be higher than those treated medically. Peet *et al.* (14) state: "The rationale on which we base our operative procedure is . . . the relief of renal ischemia by interruption of the sympathetic vasoconstrictor outflow to the kidneys"

Foa *et al* (17) measured effective renal blood flow and filtration rate by

group of 27 patients. Adson based his theory for the operation on the fact that the blood pressure drops following spinal anesthesia, and designed it to denervate and interrupt vasoconstrictor stimuli to a large vascular bed including the adrenal glands and kidneys. Page and Heuer (6,7) treated patients by this operation with similar results. They too wished to abolish extensive vasomotor control over the splanchnic area since they considered it an important, though not the only, reservoir governing the level of the arterial pressure. A review of later results by Heuer and Glenn (8) is given in Table I. Ventral root rhizotomy is an extensive and hazardous procedure, and both Adson and Heuer abandoned it in favor of a direct approach to the sympathetic nerves and ganglia.

Subdiaphragmatic Splanchnicectomy with Resection of the First and Second Lumbar Ganglia. Craig first performed this operation in 1932 and Adson has employed it consistently since 1935. The incisions, the defect in the sympathetic chains, and the area of denervation are shown in Figure 1. In a review of the results and the indications for the operation Adson (9) states: "Psychic stimuli integrated with vasomotor phenomena undoubtedly exert a powerful influence on the vascular tone of the smaller arteries and arterioles. These stimuli may be chiefly responsible for the early stages of essential hypertension." He states further that, "if surgical intervention in the form of sympathectomy is to be performed it must be done in the early phase of the disease, before fixed changes take place in the peripheral circulation."

Allen and Adson (10) state: "Sympathectomy is not carried out because we have assumed that the increased resistance to the flow of blood is localized to the splanchnic region. On the contrary, we accept the evidence that the increased resistance offered to the flow of blood through the arterioles is present over the entire body. If the surgeon is to accomplish the best results . . . he should sever the connections of the sympathetic nerves with almost all portions of the body." They conclude: "Our experiences justify continuance of the operation in the treatment of essential hypertension. The individuals who will receive the most benefit from [illegible] the course of their

[illegible]son (11), Bartels, Poppen, and Richards (12), Bordley, Gladston, and Dandy (13) and others report varying degrees of improvement, palliation, or failure after this procedure.

Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Gangli-

nicectomy "gives better results when hypertension is due to a spasm of the arterioles or to a mild, reversible degree of hypertrophy of the muscle fibers in the media, and not when severe permanent anatomical lesions have transformed the majority of the arterioles into narrow and rigid tubes."

Page and Heuer (19), Davis and Barker (20), White and Smithwick (21), Rytand and Holman (22), Ayman and Goldshine (23) and others have reported that their results after supradiaphragmatic splanchnicectomy occasionally were good, but more frequently they were temporary, poor, or indifferent.

Lumbodorsal (Thoracolumbar) Splanchnicectomy Smithwick (24) developed the operation illustrated in Figure 3 in 1938 and has since employed it in more than 700 patients His earlier experiences with supradiaphragmatic and subdiaphragmatic splanchnicectomies revealed that they "did not consistently produce significant postural changes or produce comparable blood pressure changes in similar cases in the horizontal position." He therefore combined and extended these operations "to determine the minimal operation which would always cause a postural change in blood pressure and still fulfill the other qualifications which we felt were important." The effect of the Smithwick splanchnicectomy on the hypertensive state of 156 patients has been reported (25) and is summarized in Table I.

Castleman and Smithwick (26) report a study of the blood vessels in 100 renal biopsies obtained during operation The biopsies of 7 patients showed no disease of the blood vessels, 21 showed minimal and 25 moderately advanced vascular disease, while 33 biopsies showed severe and 14 extremely severe renal vascular disease The authors correlated these observations with the other evidences of hypertension and with the effect of sympathectomy They conclude that. "the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension and that in many of these and probably others the hypertensive state antedated the renal vascular lesion . . . These observations are not in keeping with the concept that renal ischemia due to preexisting renal vascular disease is the cause of essential hypertension in man"

Smithwick has summarized his more recent experiences with sympathectomy for hypertension in a personal communication to the author:

"Approximately 60 per cent of the patients have had what we consider to be a significant improvement on the basis only of a lowering of the diastolic pressure. A somewhat larger percentage appear to have obtained a worthwhile result as evidenced by postural hypotension and changes in eyes, heart, kidneys, and symptoms.

diodrast and inulin clearances in 17 patients before and after bilateral supradiaphragmatic splanchnicectomy and found that the operation did not change the renal blood flow significantly even in the 8 patients whose blood pressure was reduced. They concluded that decreased vascular resistance

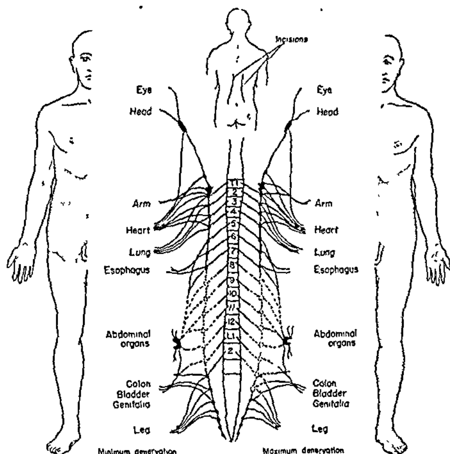


FIG 3. Lumbodorsal splanchnicectomy—Smithwick

and intrarenal arteriolar vasodilatation occurred in the 8 patients with reduced blood pressure and unchanged renal blood flow, and suggested further that the pulse pressure within the kidney may have increased. The hypothesis of these authors is: "reduced intrarenal pulse pressure, and not renal ischemia, is a causal factor in human hypertension." Foa, Foa, and Peet (18), in a study of preoperative biopsies of skeletal muscle in 350 consecutive patients observed that the supradiaphragmatic splanch-

Drs E. S Orgain, C. Johnston, W. B. Anderson, W. Kempner, and others have facilitated study of the later group. All patients had a trial period of medical therapy and rest before operation. The effect of the operation in 41 patients treated from 18 to 76 months ago, determined by examination

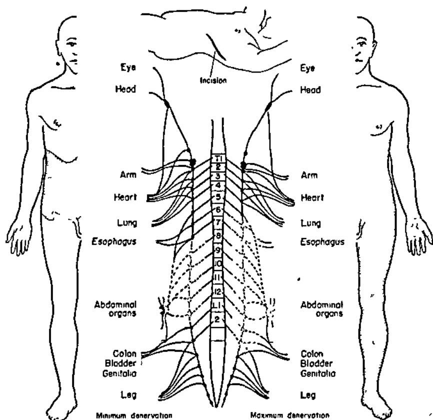


Fig 4 Lower thoracic paravertebral sympathectomy, splanchnicectomy, and celiac ganglionectomy — Grimson

during office visits and required return admissions to the hospital, is summarized in Table I

Subtotal to total paravertebral sympathectomy was begun because of evidence derived from many experiments including partial, splanchnic area, and total sympathectomy in normal dogs and in dogs with experimental neurogenic and renal hypertension

The operation is purposely varied according to the severity of the hypertension, the age and sex of the patient, and the character of the physiological abnormalities observed. The adrenal glands are carefully inspected and tumors removed if found to be present. The operative mortality in the last 300 consecutive cases is approximately 1 per cent." He states further: "It is my feeling that the sympathetic nervous system is an active causative factor in most cases of so-called essential and malignant hypertension Most patients have an abnormal vasomotor mechanism which in the majority involves a large portion of the vascular bed. The operation results in decreased tone of smooth muscle in the visceral vascular bed in particular. All of our data seems to point to the extra-renal visceral vascular bed as being the area which is affected principally. The renal vascular bed is probably also affected to some degree Vascular disease is not a causative factor of major importance in hypertension. Most of the vascular damage seen at death probably develops after the hypertension"

Smithwick has added upper thoracic sympathectomy in a few cases that did not respond satisfactorily to the lumbodorsal procedure, but has observed no further improvement

De Takats, Heyer, and Keeton (27), Bartels, Poppen, and Richards (12), Ayman and Goldshine (23), and others describe their experiences with the older splanchnicectomy technics and their adoption of the lumbodorsal or transdiaphragmatic splanchnicectomy of Smithwick. Hinton (28) reports a favorable effect following this procedure in 40 patients.

The author has had no personal experience with the operations of Adson or Peet Hypertension has been treated in 18 patients by excision of the lower five, six, or seven thoracic ganglia, the first, or first and second, lumbar ganglia, the available length of the splanchnic nerve, and in addition in 6 of the 18 patients by excision of the celiac ganglia. The operation was carried out either through the posterior hockey-shaped incision, as used by Smithwick in his earlier cases, or through the lateral transthoracic approach illustrated in Figure 4, the latter being preferred. The effect of the splanchnicectomy in 14 patients treated from 18 to 54 months ago is summarized in Table I. Lowering of blood pressure occurred in 5 patients. In general, the degree of lowering of pressure or improvement of the patient was considerably less than that observed after the more extensive sympathectomy described in the next paragraphs.

Subtotal to Total Paravertebral Sympathectomy, Splanchnicectomy, and Celiac Ganglionectomy Use of the operation illustrated in Figure 5 was begun in 1940 at the University of Chicago (4,29) and has been continued since 1942 at Duke University The cooperation of Drs A. S. Alving, Wright Adams, J Gans, M Landowne, and others have made possible detailed observation of the earlier group of patients The cooperation of

section of the modulator nerves. Various types of localized sympathetic denervation have not prevented either of these types of neurogenic hypertension It therefore seems likely that better results may be expected from total sympathectomy than from partial sympathectomy directed toward localized vascular beds, such as the splanchnic area."

In an earlier review of the surgical treatment of hypertension in patients (4) the author stated:

"In general the lowering of blood pressure observed has been directly proportional to the extent of the sympathectomy and inversely proportional to the severity of the disease. . . . It seems probable that sympathectomy should be employed early in the disease when possible It also seems probable that extensive sympathectomy may be of value in many patients in a later and more hopeless stage"

Increasing experience with sympathectomy in hypertensive patients has served to substantiate my opinions, as expressed above.

Celiac Ganglionectomy Crile was a pioneer in the field of surgery for hypertension His early operations included unilateral adrenalectomy, bilateral denervation of the adrenal glands, and splanchnicectomy. He later resected the celiac ganglia, interrupted the "adrenal-sympathetic complex," and denervated the aorta. This last operation, celiac ganglionectomy, was performed upon 234 patients (33) Varying degrees of objective and symptomatic improvement are noted. The systolic blood pressure was reported as reduced 40 points or more in 42 9 per cent of the patients and the diastolic 30 points or more in 35.7 per cent Crile's interest in the adrenal glands and the celiac and adjacent periaortic sympathetic nerves and ganglia grew out of his studies of comparative anatomy. It is interesting that removal of these ganglia probably blocked nerve regeneration more effectively than some of the currently employed technics for splanchnicectomy

Surgical Concept of Hypertension

Hypertension is usually a complex disease process. It seems well established that the elevation of blood pressure in cases of hypertension is effected by an increased peripheral resistance to the flow of blood offered by the smaller blood vessels of the entire body There are no consistent changes of cardiac output, blood viscosity, or blood volume. The increase of peripheral resistance may be caused by an abnormal central or reflex vasoconstrictive tone via the sympathetic nervous system, by humoral vasoconstrictors traveling in the blood stream, or by disease of the smaller blood vessels

It was found that in normal dogs (30) a decline in blood pressure follows complete sympathectomy. Restoration begins within a few weeks and reaches the preoperative level in an average time of six months .... Partial sympathectomy in the form of complete and sympathetic heart denervation, and preganglionic denervation of splanchnic area did not greatly handicap the vasopressor system, as

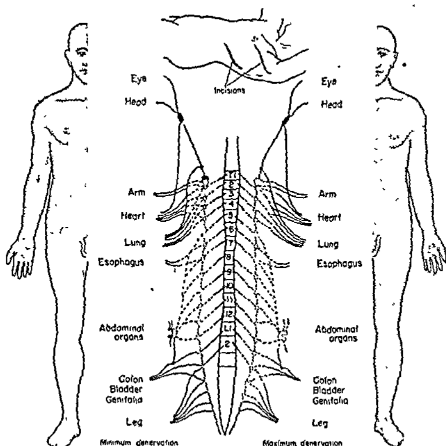


Fig 5. Subtotal to total paravertebral sympathectomy, splanchnicectomy, and celiac ganglionectomy — Grimson

shown by their failure to lower blood pressure, or to appreciably alter the response to increased intracranial pressure In dogs with experimental hypertension (31, 32) the author concluded: "The importance of the splanchnic area seems to have been overemphasized. . . . In a previous report it was demonstrated that total sympathectomy prevents the pressor response to increased intracranial pressure . . also prevents or abolishes for a time the elevation of blood pressure that follows

on Experimental Hypertension" (36), and will not be included in this report. Page and Corcoran (37) have presented their theory and that of the investigators actively interested in a humoral pathogenesis of hypertension, and have related it to medical and surgical therapy. Peet (14), de Takats (27), and some other surgeons believe that the renal hypertension mechanism is of primary importance. The great majority of the surgeons quoted above, and the author, feel that the benefit derived from sympathectomy is little, if at all, through changes of renal circulation Renal circulation in patients before and after sympathectomy has been studied by several investigators, who have not found any consistent change. Furthermore, sympathectomy does not prevent the constriction by angiotonin or hypertensin of denervated vascular beds elsewhere in the body. Efforts to decapsulate the kidneys and produce collateral blood supply by grafts of muscle or omentum have afforded little encouragement

There is as yet no generally recognized or clinically applicable tissue extract treatment for renal hypertension. Another approach to the renal problem is being investigated by Kempner (38). He has treated patients with a rice, sugar, fruit, and fruit juice diet, supplemented by vitamins and iron and often by fluid restriction and weight reduction. The diet is planned "to compensate renal metabolic dysfunction by replacing the ordinary mixed diet " Kempner's working hypothesis is that the ordinary mixed diet may contain constituents that increase the kidneys' production of harmful substances which, he believes, may play a role in the development of hypertension, vascular retinopathy, encephalopathy, heart lesions, and new kidney disease. Kempner reports remarkable subjective and objective improvement and lowering of blood pressure in approximately 60 per cent of his patients with hypertension, particularly those that also have uremia. It is a treatment and not a cure of hypertension, since it may fail entirely and since many patients after varying periods of time discard it and seek other treatment. Unfortunately, neither this dietary regimen nor the tissue extracts have furnished a specific treatment by which the exact importance of the renal factor in the hypertensive patient can be determined Encouraging results after extensive sympathectomies, however, seem to indicate that in many patients the renal factor, if present, is not sufficiently important to prevent lowering of blood pressure, disappearance of hypertensive retinitis, and other objective improvements.

Increase of the peripheral resistance may also be caused by generalized arteriolosclerosis. Routine biopsies of muscle by Foa, Foa, and Peet (18), and of kidney by Castleman and Smithwick (26), during operations for hypertension have provided valuable information Arteriolar disease was

The sympathetic nervous system, with its control of vasoconstriction, its control of liberation of epinephrine and sympathin, and to a considerable extent its control of heart rate, is the only important known mechanism capable of effecting, on a reflex basis, a "neurogenic" or "central" type of hypertension. These terms are employed by many physicians for patients with persistent elevation of blood pressure and evidence of vasomotor instability. Such patients may later develop retinitis, altered renal function, or vascular disease. The author (31) has reviewed the animal experiments demonstrating that interruption of the modulator or buffer nerves of the carotid sinus and the heart and aorta will produce a high and enduring elevation of blood pressure. These nerves, acting through the vasomotor centers, balance central psychosomatic vasopressor stimuli, and in normal animals and man maintain normal blood pressure. Although the modulator mechanism is still active in individuals with hypertension, it is apparently readjusted to a higher level of blood pressure. Physicians have long employed rest, sedation, reassurance, and varying degrees of personal psychotherapy for hypertension. It is evident from the quotations from various authors in the paragraphs above that surgeons also consider the "neurogenic" factor of major importance in hypertension.

Humoral vasoconstrictors may increase the peripheral resistance and elevate blood pressure Crile (33) early stressed the importance of epinephrine. Every surgical procedure currently popular denervates the adrenal glands Epinephrine, however, is not considered important except in cases of hypertension with active tumors of the adrenal medulla Little is known of the clinical significance of sympathin. Chang (34) has suggested that a vagus reflex may activate the posterior lobe of the pituitary gland and elevate blood pressure by liberating its pressor hormone. Hildebrand and Rynearson (35) in their review of the literature find evidence suggesting that a hyperfunctioning posterior lobe of the pituitary might be important in hypertension associated with eclampsia. The role that pitressin-like substances might have in maintaining peripheral resistance is not clearly established.

The kidneys have in recent years received major attention as the source of a humoral vasoconstrictor. Angiotonin or hypertensin is a pressor agent that originates when circulation or pulse pressure through the kidney is altered, with resultant anoxemia The process by which renin interacts with renin activator or hypertensinogen to produce angiotonin or hypertensin seems to be enzymic The concept of the biology of this mechanism and the therapeutic efforts with tissue extracts to block or neutralize it in hypertensive patients have been thoroughly reviewed at a recent "Conference

of hypertension consistently. In any event, the effect upon the circulation as a whole will depend upon the extent of the sympathectomy.

Another purpose of sympathectomy is the production of a postural hypotension. Of the forms of sympathectomy illustrated in this monograph, all except the supradiaphragmatic splanchnicectomy (Fig. 2) are sufficiently extensive consistently to cause postural hypotension. The sympathetic nervous system is the efferent pathway of the complex neurovascular proprioceptive mechanism that reflexly regulates the flow of blood during changes of activity and posture. Removal of the control over the vessels of the splanchnic area and the dependent portions of the body results in a reduced blood pressure when the patient stands or is active. There is a compensatory overactivity of the remaining sympathetic nerves to the upper portions of the body that often produces pallor, sweating, and tachycardia. Interruption of the control to the upright portions, or to all of the body as well as to the splanchnic area (Fig 5), results in a postural hypotension with bradycardia or normal heart rate and with less disability, particularly if some vasoconstrictor fibers to the legs are left.

The major purpose of sympathectomy is to correct or reverse the hypertensive disease process. Although this cannot be entirely accomplished, since some degree of vascular damage will have developed in each patient before surgery is indicated, it can be nearly accomplished, as illustrated by the reduction of blood pressure to normal or nearly normal of more than 96 of the patients reported by various authors (Table I, page 174) Another major purpose of sympathectomy is to arrest or delay the development of the hypertensive disease process This can often be accomplished in patients with definite vascular disease, as evidenced by damage to the eyes, brain, heart, or kidneys The major purposes of sympathectomy will be more readily achieved as the operations are made more extensive, as patients are referred for surgery earlier in the course of the disease, and as medical means of combating vascular disease and the renal humoral mechanism are developed

Limitations of Sympathectomy

The physician and the patient should consider the surgical treatment of hypertension as a choice between two evils. The discomfort, disability, and risk to life that are associated with a progressive hypertension resistant to medical treatment are well recognized Discomfort, disability, operative risk, and a chance of failure are also associated with sympathectomy. Nerve fibers carrying vascular and visceral pain travel through the paravertebral sympathetic chains and the splanchnic nerves The chains are

minimal or absent in the early stages of the hypertensive disease process, and advanced only in the later stages of the disease. It would seem that arteriolar sclerosis follows and develops along with the hypertension process, and Castleman and Smithwick believe that it does not ordinarily initiate the disease

It is probable that many patients referred for sympathectomy already have a neurogenic disturbance affecting regulation of blood pressure, a vascular disease in the kidneys or throughout the body, and other as yet unknown physiologic or pathologic processes all contributing to the hypertension. The sequence in which these several components develop and the relative importance of each at the time of treatment is important, but not easily evaluated Accumulating evidence seems to indicate that the "neurogenic" component is at least a major initiating and perpetuating factor in many patients The renal component is probably important when hypertension develops during or after a primary kidney disease. It may also be important late in the hypertensive disease process as the kidney is injured by the high blood pressure and as vascular disease develops. The vascular disease component itself seems to be a result of, rather than a cause of, hypertension

Purpose of Sympathectomy

The several forms of sympathectomy were all designed to supplement the medical management of hypertension by decreasing the resistance to the flow of blood in major areas of the body The splanchnic area was first selected because of its size and because its denervation included the kidneys and interrupted reflex liberation of epinephrine Peet (14) and some others by their operation intend to denervate the kidney and decrease peripheral resistance throughout the body by altering the renal humoral mechanism. Adson, Heuer, Smithwick, the author, and many others believe it unlikely that the renal mechanism can be significantly altered by denervation of the kidneys, and that the purpose of surgery should be the denervation of as large an area of the body as is considered necessary or advisable

Sympathetic denervation of large areas of the body may relax the vascular bed by blocking normal vasoconstrictive tone and control, a nonspecific effect which might somewhat benefit patients with advanced vascular disease. In addition, such denervation may block abnormal vasoconstrictive tone and control in patients with a neurogenic variety of hypertension, an effect which would be specific Experimental evidence indicates that sympathectomy must be complete, i e , involving the heart as well as the splanchnic area, in order to lower the blood pressure in this type

ably not clinically significant, particularly after denervation of the adrenal glands by splanchnicectomy has arrested liberation of epinephrine. The influence of metabolic products such as lactic acid and carbon dioxide and of humoral substances such as pituitrin, sympathin, or angiotonin or hypertensin, if present, seems more important Sympathectomy, therefore, improves circulation more by blocking normal or abnormal vasoconstrictive tone than by relaxing the peripheral vascular bed

Preganglionic and postganglionic sympathetic nerves may regenerate Regenerating fibers follow along scar tissue Regeneration after extensive or total paravertebral sympathectomy is largely preganglionic and is probably dependent upon the celiac and other outlying ganglia for connection with postganglionic fibers and cells connected to the vascular bed. Splanchnicectomies of the types shown in Figures 1 and 2 (pages 175, 177) probably allow extensive late functional regeneration One may minimize this late regeneration following sympathectomy by extending the area of removal of the paravertebral chain ganglia (Fig 3, page 178) and also by excising part or all of the celiac ganglia (Fig 4, page 181, and Fig 5, page 182).

Indications and Contraindications for Sympathectomy

Sympathectomy is often indicated as a supplement to the medical management of patients with hypertension The primary aim of both surgical and medical treatment is reduction of blood pressure to prevent or delay serious damage to the blood vessels throughout the body and particularly to those of the heart, brain, and kidney Operative procedure is then best indicated in young patients with a rapidly rising blood pressure and little evidence of vascular disease It is also well indicated, though less urgently, in young patients with a slowly progressive increase of blood pressure. Sympathectomy should be delayed until several methods of medical treatment have been tried and thorough cardiac, renal, and vascular studies have determined the progressive nature and seriousness of the disease, but it should not be delayed so long that an irreversible disease process develops The risk of operative mortality in milder forms of hypertension is low

Many patients present themselves for treatment only after serious vascular, cardiac, or renal damage has occurred Surgery may be indicated for some of them, but reduction of blood pressure to normal or near normal values can be accomplished only occasionally More frequently, sympathectomy results in some reduction of pressure, a postural hypotension, disappearance of retinal hemorrhages, exudates, and papilledema, decrease in the size of dilated hearts, and relief of symptoms Encouraging results

also closely associated with segmental somatic intercostal and lumbar nerves. Excision of the sympathetic nerves is followed by a neuritic type of pain, maximal during the first several months after sympathectomy but diminishing thereafter *It seldom lasts longer than six months to a year.* Postural hypotension often prevents normal activity during the first several months after sympathectomy. Sweating occurs in areas of the body that are not denervated and may be excessive and inconvenient for several months. Ejaculation of seminal fluid is decreased and sterility may occur *in the male patient. Libido, sexual ability, and orgasm are not altered in* either the male or female. These disabilities are common to all of the operative technics illustrated in Figures 1 through 5 Fortunately, a gradual compensation occurs and after three to twelve months the patient usually has little difficulty. Additional disabilities peculiar to individual operative technics will be discussed further on page 190

The immediate risk to life of the operative procedure and the chance that relief of the hypertension will fail are summarized in Table 1. Risk and failure depend upon the severity of the vascular disease present at the time of operation and on the type or the extent of operation Probably the most important limitations of sympathectomy are inherent in the anatomic and physiologic processes that govern the tone and activity of the vascular smooth muscle early and late after denervation. These have been reviewed in an earlier work (39) and will only be summarized here.

The sympathetic nervous system is responsible for regulation or modulation of the tone of smooth muscle in peripheral blood vessels but only little responsible for maintenance of this tone Sympathetic regulation or modulation may be either vasoconstrictive or vasodilative. Increase of circulation will be less evident in an organ receiving preponderantly vasodilative sympathetic control than in one that receives a major vasoconstrictive influence This is well illustrated by the increase in blood flow after regional sympathectomy of a leg compared with the slightly decreased blood flow, as judged by cardiac output, following sympathectomy of the entire body

The smooth muscle of blood vessels is able to develop and maintain an independent tone even though deprived of all nervous and humoral influences. For several days or a week this tone may approach or equal that present under normal conditions The increased responsiveness of smooth muscle to epinephrine after central nervous modifying or buffering influences have been eliminated by preganglionic sympathectomy, or to a somewhat greater degree by ganglionectomy, has been considered to be the reason for increases of peripheral vascular tone. This phenomenon is prob-

Adequate exposure of the sympathetic nerves often requires division of more than one of the lower thoracic and upper lumbar segmental nerves Division of two or more of the somatic nerves corresponding to T 11, T 12, L 1, and L 2 will paralyze some portion of the muscles of the abdominal wall and may necessitate the use of an abdominal binder or corset. The approach of Adson or Smithwick has the advantage that the adrenal glands and kidneys may be routinely examined Occasionally, unsuspected tumors have been found and removed

The author now employs only the transthoracic approach for splanchnicectomy (Fig 4, page 181), or subtotal to total sympathectomy (Fig. 5, page 182). This involves minimal injury to somatic nerves and muscles and ready and adequate exposure of the sympathetic nerves and ganglia. The diaphragm may be detached posteriorly and retracted, to afford access to the upper lumbar ganglia, or incised, if indicated, to expose the adrenal glands Subtotal to total paravertebral sympathectomy and celiac ganglionectomy is my method of choice for most of the patients considered candidates for surgical treatment A bilateral Horner's syndrome occurs, but this has not been objectionable Splanchnicectomy is now used only in patients considered poor operative risks because of cardiac status, age, or temperament

Evaluation of Effects of Sympathectomy

It is difficult to evalu[illegible]
sion. Wagener and Ke[illegible]
Rojas, Smithwick, and [illegible]
to classify hypertensive patients or to compare or control the results of surgical and medical treatment These attempts have not been too successful, patients present individual problems and are not easily grouped and classified, and the bases for selection of patients for operation are varied A study of medical and surgical treatment should not attempt to determine which is the better method It should rather determine whether or not, or when, surgery should be employed to supplement medical treatment. Sympathectomy has received its support largely from physicians who have observed more than a few patients before and after operation, and who have been able to determine that varying degrees of improvement can be achieved.

The difficulties encountered in efforts to evaluate treatment of hypertension are well illustrated by the reports condensed in Table I (page 174). The several series of patients presented cannot be compared individually, and the table is of value only as an approximate, general view of the prob-

are most likely in patients with an acute exacerbation or a malignant phase of an otherwise slowly progressive disease process. They are least likely in patients who have slowly reached a very high systolic and diastolic blood pressure. The operative risk and the chance that sympathectomy may not afford worth-while benefit increases with the severity of the hypertension Surgery is not indicated in some patients with advanced disease since it may add unnecessary discomfort and shorten life expectancy.

Contraindications for surgical intervention in hypertension are (*1*) an elevated nonprotein nitrogen in the blood; (*2*) infarction of the heart muscle; (*3*) age of patient (over 50); (*4*) difficult personality problems or fixed neuroses, alcoholism, or morphine addiction; (*5*) encephalopathy with increased intraspinal fluid pressure. Hypertension originating some years previously in an acute kidney disease or toxemia of pregnancy does not constitute a contraindication to surgery, since the residual hypertension may not be renal and often responds to sympathectomy. The occurrence of a cerebral vascular accident is likewise no contraindication to operative procedure.

It is evident that the indications for sympathectomy are not clearly definable and that the stage in the disease process at which obvious disadvantages offset possible advantages is not easily determined. A decision to operate should be made only after thorough cardiac, vascular, and renal examination At present, there are no specific clinical tests that can alone determine the relative importance of neurogenic, vascular disease, or renal humoral components Rest, the sodium amytal test, and the effect of anesthetic agents on blood pressure are not specific and do not provide a surgical prognosis (40) Gans (41), in his article on the significance of changes in the fundi oculi proposes a classification for differentiating the sclerotic from the acute hypertensive changes Examination of the fundus is certainly one of the most important of the many factors to be considered when evaluating the hypertensive patient

Selection of Operative Procedure

There is no general agreement on the operative approach which should be employed.. The splanchnicectomies of Adson (Fig 1, page 175) and Peet (Fig 2, page 177), survived early skepticism and demonstrated that surgery had some value. Many surgeons now believe that Smithwick's splanchnicectomy (Fig 3, page 178) is accomplishing more consistent reduction of blood pressure and clinical improvement These splanchnicectomies are all approached through posterior incisions which have the disadvantage of requiring deep dissection through heavy muscles and fascia

alone, 426 were as resistant to surgery as they had been to medical treatment. Some symptomatic relief and clinical improvement occurred in many of this group. These results were accomplished with an over-all operative death rate of 37 of the 950 patients, or 3 9 per cent. It should be noted that this mortality is largely a result of the efforts of several surgeons to help seriously ill patients. Aside from the 37 operative deaths, 191 patients and an unreported number from the Smithwick series died during the period of observation after the operation, death usually occurring from complications of the hypertensive disease process With the passage of time, complications will take other patients of this group It seems probable that some of the patients whose blood pressures were reduced to normal will at some time again show hypertension Surgeons will have to rely on improvements in medical therapy which will eventually be developed for other components of the hypertensive disease process before combined medical and surgical efforts can effect a cure

Conclusions

Sympathectomy offers some aid to the physician in the treatment of many patients with hypertension The belief is growing among surgeons that surgical technic should be directed toward sympathetic denervation of increasingly extensive portions or of the whole body The results of sympathectomy seem to be inversely proportional to the severity of the disease process and directly proportional to the extent of the operative procedure Young patients with early and progressive hypertension are the best subjects for treatment, but older or more seriously ill patients may also be benefited although the results will be less encouraging and the operative risk greater

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lem. Allen and Adson (10) have in general treated moderately ill patients, which probably explains their low operative mortality of 1 in 224 Some patients who were refused operation because of the extent of the disease, might well have been benefited without greatly increasing the risk of operative death. Peet, Woods, and Braden (14) operated on patients in all stages of illness, and their operative mortality—12 in 350—is probably justified by their rate of salvage of ill patients The results reported by these authors have been criticized because many of the postoperative studies are based on occasional examinations in the office, with blood pressures often taken only in the sitting position. Rytand and Holman (22) have demonstrated the discouragement that may occur when splanchnicectomy is limited almost entirely to patients with advanced disease. Heuer and Glenn (8) have presented a good general view of the late results of three forms of splanchnicectomy They believe that sympathectomy has some value, but they emphasize that it does not cure the patient, 26 of their 57 patients having died at some time after operation Bartels, Poppen, and Richards (12) were discouraged by the supradiaphragmatic splanchnicectomy but now believe that more extensive sympathectomy may have an ameliorating effect upon blood pressure These authors suggest an age limit of 40 Ayman and Goldshine (23) have carefully followed 14 patients treated by splanchnicectomy and have concluded that "no medical therapy has ever equaled the results obtained in 5" The report of Smithwick (25) is evidence that increasing the extent of the sympathetic denervation can improve the results of surgical treatment

Of the 14 splanchnicectomies in my series, 5 were performed in patients that would not have been considered for the subtotal or total sympathectomy The drop in blood pressure and the clinical improvement in the remaining 9 did not equal that achieved in 29 of the 41 patients treated by the more extensive sympathectomy Observation of each of my patients has been facilitated by hospitalizing them for periods of examination of about a week. Hospital admissions are required 3 months after operation and subsequently at yearly intervals.

Several observations seem warranted if one accepts and summarizes all of the reports in Table I Of a total 950 patients, most of whom at the time of operation were resistant to medical treatment or were suffering from gradual elevation of blood pressure, 96 and some of those reported by Smithwick but not enumerated maintained a reduction of blood pressure to below 150/100 or to normal In addition to many of the 124 patients with lowered blood pressure reported by Smithwick, 221 showed reductions considered significant by the several authors Judged by their blood pressure

Surgical Treatment of Tumors and Chronic Inflammation of the Lung

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Tumors

In the last ten to fifteen years the definitive surgical treatment of primary tumors of the lung has yielded satisfactory results. This method, as has been so frequently pointed out, is the fruition of the precocious development of thoracic surgery since World War I.

Adams (1), and others, have suggested that the chief factors contributing to this development have been (*1*) better comprehension of the physiologic principles involved, (*2*) the development of a satisfactory technic for the resection of lobes or of the entire lung, and (*3*) improved diagnostic procedures. These factors include the development of differential pressure anesthesia, the individual dissection and ligation technics of pulmonary and lobar resections, and the perfection of bronchoscopy, bronchography and roentgen technics. The improvement of results in the surgical treatment of primary pulmonary tumors may be ascribed to them.

A wide variety of primary tumors of the lung has been described in the literature. Graham and Womack (2,3) have proposed the interesting and arresting thesis of a common origin of many tumors from the failure of embryonic bronchial buds, which consist of both entoderm and mesoderm, to develop into normal structures. It seems reasonable to these authors to consider that tumors might appear in adult life which had their origin in either of the two primitive germ layers. In accordance with this thesis, two main groups of pulmonary tumors can be thought of as occurring from a failure of a bronchial bud to develop into a normal adult arrangement of tissues: (*1*) *those in which the mesodermal elements predominate, and* (*2*) those in which the entodermal (or epithelial) elements are dominant. The former group would include tumors commonly known as chondroma, osteoma, fibroma, lipoma, angioma, myxoma, and sarcoma. The second group is illustrated chiefly by the so-called adenoma. Such a hypothesis, according to Graham and Womack, would explain the extremely frequent

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result of its location, when it grows large enough to be obstructive, atelectasis of a lobe, lobes, or of the entire lung occurs; if the obstruction persists, secondary bronchiectasis, or suppurative pneumonitis, or both, follow The tumor appears most often in the second and third decades of life, and it is found somewhat more frequently in females than in males, in contrast to the well-known preponderance of bronchogenic carcinoma in males

Viewed bronchoscopically, the tumor presents a fairly characteristic appearance of a succulent, pink, rounded outcropping of tissue protruding into the lumen of the bronchus. The largest part of the tumor, however, may be deceptively outside the lumen. Biopsy is usually a simple matter, *the diagnosis most often being made by its means. The tumor is vascular*, so that hemoptysis is a common symptom, and not infrequently it is associated with other congenital anomalies of the lung

Graham and Womack (2) state

> "The resemblance to fetal lung which some of these tumors exhibit is often so striking that it would be extremely difficult, if not impossible, to distinguish one from the other on the basis of microscopic sections. This close resemblance probably furnishes a clew to the origin of these tumors in that it suggests that they are derived from disorganized embryonic bronchial buds which have failed either to pursue a normal development or to have atrophied The position of these tumors in the walls of the larger bronchi is also suggestive of such an origin."

They believe that these tumors satisfy all of the criteria of malignancy—invasion of adjacent tissues, involvement of regional lymph nodes, and metastases to distant organs—and present convincing evidence that such tumors become malignant.

Konzelman, on the other hand, states "That these tumors *may* undergo malignant change must be admitted, although I have not encountered such a change, nor have I seen a malignant tumor which I believe started as a benign adenoma" (6). Other pathologists concur in this opinion. Alexander (8) agrees with Graham's theory of malignancy and asserts that Weller has for many years insisted that the so-called adenoma is a Grade I carcinoma

In order to include those cases which have not exhibited malignant characteristics, Graham (2) concedes that many of these tumors, when first seen, are benign to the extent that there may be no demonstrable evidence of any of the commonly recognized criteria of malignancy He also agrees that many patients with a bronchial adenoma may live their normal life span before the tumors become malignant However, as he points out, it is a striking fact that bronchial adenoma is rarely found at autopsy, es-

occurrence of epithelial elements in so-called chondroma of the lung and of mesodermal elements in the epithelial tumors.

It is true that in attempting to arrive at a precise diagnosis in a given case of thoracic tumor demonstrated, for example, by the roentgenogram, one may pass through a certain differential diagnosis by following various classifications. Nevertheless, the fact remains that such mental evolutions are largely philosophic; the diagnosis can be proved only on the basis of the histopathology.

Purely benign tumors of the lung are so rare as to deserve little consideration in this discussion. For all practical purposes, when we discuss primary tumors we mean bronchogenic carcinoma. Alexander (4) states that despite the prevailing impression, most *circumscribed* intrathoracic neoplasms are intrapulmonary and malignant. In this connection, the oft-quoted surgical maxim "no tumor is a good tumor," is particularly applicable to the thorax Today, when the diagnosis is in doubt, exploratory thoracotomy may be undertaken with no more risk than is entailed in exploratory laparotomy, and with a resultant salvage of patients otherwise condemned by a policy of procrastination.

The so-called bronchial adenoma has received considerable attention in the past decade, in contrast to its previous obscure existence, and therefore, deserves consideration In the light of its recognized, relatively frequent occurrence, and the necessity in many instances for its inclusion in the differential diagnosis, it will be particularly considered at this point.

Bronchial Adenoma

Literature dealing with bronchial adenoma has begun to appear increasingly, at the 1944 meeting of the American Association for Thoracic Surgery, the presentation of several papers on this subject led to considerable discussion For the most part, the controversy centers around the question of whether the tumor is benign, malignant, or potentially malignant

Some idea of the frequency of occurrence may be gained from the figures reported by various authors Thus, Adams (5) states that of 175 cases of primary tumors of the lung studied at the Massachusetts General Hospital, 17, or 10 per cent, were bronchial adenomas Jackson (6) was able to find 20 cases of bronchial adenoma in reviewing his series of bronchial tumors, and Chamberlain and Gordon (7) have reported on 10 cases

The general characteristics of the tumor are now well known In the vast majority of instances, it occurs in a major bronchus, or sufficiently close to it, so that the tumor may be visualized bronchoscopically As a

There remains the decision as to which operation to perform: lobectomy or pneumonectomy. My own practice has been to decide on the basis of the location of the tumor and the extent of secondary pulmonary infection or damage, although the two factors are almost always in agreement, since the second is the result of the first. In other words, if the adenoma is so located that it may be completely removed by lobectomy, as demonstrated by bronchoscopy and at the time of operation, I believe this to be the operation of choice, since it conserves pulmonary tissue and avoids certain of the postoperative physiologic readjustments peculiar to total pneumonectomy. If, however, the tumor is located in or involves the main stem, there is no choice, and pneumonectomy must be performed.

Maier (9) mentions an interesting subgroup of adenomas, exhibiting a somewhat higher incidence of malignant characteristics, 50 per cent of which have been either close to the carina, projecting into the trachea from the bronchus, or arising in the tracheal wall As a result of their location, the mortality from tumors in this particular subgroup has been much higher than in ordinary bronchial adenomas, a number of patients dying from tracheal obstruction

Graham (2) believes that lobectomy can at times be adequate, but that often (as noted above) it is inadequate because of the location of the tumor. He prefers total pneumonectomy since it permits removal of possibly involved regional lymph nodes at the same time. In patients who are a good risk, there is little, if any, greater danger from total pneumonectomy than from lobectomy.

Bronchogenic Carcinoma

The increasing frequency with which cancer of the lung has been reported as a cause of death in recent years has aroused considerable speculation as to whether this denotes a real change in incidence of this form of malignant neoplasm, or whether it is merely the result of improved diagnostic methods combined with more careful search for a disease attracting attention because it is reported more frequently than in the past Dorn (10) states that between 1914 and 1930 the death rate from cancer of the lungs and pleura increased by nearly 400 per cent, as compared with a total increase of 20 per cent for all forms of cancer There was a sex difference in the change, being 450 per cent for males and 260 per cent for females

From 1930 to 1940 the death rate continued to increase—by 22 per cent among white females and by 78 per cent among white males, or roughly 2 5

pecially after middle age. Most of them are found during life by bronchoscopy, while many more cases diagnosed as bronchogenic carcinoma are found at autopsy. His explanation of this discrepancy is that the majority of these tumors become malignant, and that the identity of the original tumor is lost after it has developed all the features of malignancy.

My personal experience with bronchial adenoma is limited to 5 cases, none of which has fulfilled the criteria of malignancy, in the sense in which a carcinoma is admittedly malignant. Nevertheless, I am convinced that Graham's theory, and the one held by many thoracic surgeons today, is correct.

Bronchoscopic Removal. Jackson *et al* (6) believe that forceps removal, electrocoagulation, and aspiration is indicated as the first step in all cases, and that it will be curative in some, palliative in others. Where there is atelectasis or bronchiectasis, they advise a preoperative course of bronchoscopic treatment, even if lung resection is to follow or is under consideration for a later date

However, some surgeons (2,7,8) as well as the writer, consider this treatment inadvisable in the many cases in which the bulk of the tumor is extrabronchial, making complete bronchoscopic removal of the tumor impossible The hazard of uncontrollable bleeding, furthermore, is so great as to give one pause when weighing this method against the admittedly low mortality of lobectomy or pneumonectomy. Another point that militates against bronchoscopic removal is that as a result of the bronchial obstruction bronchiectasis is likely to be present in the portion of the lung distal to the tumor. Finally, as Graham and Womack (2) point out, the tissue which has been removed by bronchoscopy may not show clear evidence of malignancy even when the tumor has already invaded neighboring tissues or regional lymph nodes

Surgical Resection. From the foregoing it may be inferred that most of the thoracic surgeons probably believe that resection of the tumor by lobectomy or pneumonectomy is the treatment of choice This is definitely my own opinion, in my series of 5 cases 2 were treated by lobectomy, 2 by pneumonectomy, while the fifth had had bronchoscopic removal at another clinic. There were no deaths Adams (5) notes that 10 out of 11 patients treated by surgical resection, or 90 9 per cent, were living and well Chamberlain and Gordon (7) report 6 lobectomies and 1 pneumonectomy, without a death Alexander (8) believes that the risks of hemorrhage, recurrence, malignant change, and the great ultimate risk of suppuration of the lung and pleura, far outweigh those of expertly performed lobectomy or pneumonectomy.

There remains the decision as to which operation to perform· lobectomy or pneumonectomy. My own practice has been to decide on the basis of the location of the tumor and the extent of secondary pulmonary infection or damage, although the two factors are almost always in agreement, since the second is the result of the first. In other words, if the adenoma is so located that it may be completely removed by lobectomy, as demonstrated by bronchoscopy and at the time of operation, I believe this to be the operation of choice, since it conserves pulmonary tissue and avoids certain of the postoperative physiologic readjustments peculiar to total pneumonectomy. If, however, the tumor is located in or involves the main stem, there is no choice, and pneumonectomy must be performed

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From 1930 to 1940 the death rate continued to increase—by 22 per cent among white females and by 78 per cent among white males, or roughly 2 5

and 8.5 per cent per year, respectively. Nearly 3 per cent of 39,970 patients with malignant neoplasm in the white population of one group studied were reported to have primary cancer of the lung.

It is estimated that between 450,000 and 500,000 persons in the United States are under treatment for cancer. Approximately 20,000 of the known cases are primary cancer of the respiratory system, of which about 13,000 are being treated for primary cancer of the lung Slightly more than 8,000 new cases of primary cancer of the lung are diagnosed and receive treatment for the first time each year.

Bloch *et al.* (11) found, as a result of routine chest fluoroscopy of 15,000 patients, that 91 or 0 6 per cent had intrathoracic neoplasms; over a third were classified as metastatic growths, and more than a fourth of the total were subsequently diagnosed as primary bronchogenic carcinoma.

A 10 year survey of autopsies at the Charity Hospital in New Orleans by Halpert (12) reveals both a relative and an absolute increase in carcinoma of the lung. Up to December 31, 1940, 12,972 autopsies were performed, 8,862 of them on persons over 1 year of age. There were 135 cases of carcinoma of the lung, 205 of carcinoma of the stomach, and 66 each of carcinoma of the biliary system and of the pancreas. A year-by-year analysis shows that whereas the incidence of carcinoma of the stomach remained about the same, the incidence of carcinoma of the lung gradually increased and during the last 2 years *exceeded* that of carcinoma of the stomach. Blades (13) states that in the 3 years, 1933–1936, there were seen at the Barnes Hospital in St Louis 62 proved cases of bronchogenic carcinoma, while during the following 3 years 117 such cases were admitted for treatment.

Steiner (14), however, studying material at the University of Chicago, found no evidence of real increase in the disease. The percentage of bronchial adenoma in 5,515 necropsies was 2 3 This tumor represented 7 6 per cent of all malignant tumors and 10 3 per cent of all carcinomas In a similar vein is the report of Johnson and Reinhart (15) on the autopsy material from the Department of Pathology at Ohio State University. They found a progressive increase in all carcinomas over a 25 year period, but no absolute increase in carcinoma of the lung.

Although there is some divergence of opinion as to the validity of an absolute increase in bronchogenic carcinoma, there can be no doubt of the importance of the disease, nor of the frequency with which it is encountered by the clinician

Diagnosis. Bronchogenic carcinoma follows the incidence of cancer in general. It occurs most frequently between the ages of 50 and 70.

but no age is exempt, and it is seen frequently in the thirties and forties. Hauser (16) reports a case in a Negro baby aged 17 months.

The symptoms and physical signs of primary cancer of the lung have no uniformity of pattern On the contrary, there is an extremely wide variation, depending in some degree upon the location of the tumor, and the stage of the disease when the patient is first seen Early symptoms due to the effect of the tumor itself, such as cough and hemoptysis, usually occur when the tumor is in relation to one of the major bronchi. Tumors occurring in the peripheral portions of the lung may be entirely without symptoms for many months, or, if they invade the pleura, the first evidence of the disease may be clear or bloody pleural effusion The prognosis for these tumors, of course, is of the poorest, because they are frequently inoperable when discovered.

Another group of symptoms is due to bronchial obstruction and infection of the bronchi and lung distal to the obstruction. The repeated "pneumonias" or "unresolved pneumonias" which are discovered in the histories of these patients should put one on guard in those instances in which an apparently straightforward pneumonia fails to do well

In view of the frequency with which the disease occurs and its insidious character in the early stages, only a concerted effort and a nation-wide state of awareness to bronchogenic cancer as a whole will result in early diagnosis for a greater number of patients, with a consequent improvement of their chances of being cured Any male of middle age or beyond who develops a cough and expectoration, with or without hemoptysis or blood streaking, and who cannot be shown to have tubercle bacilli in the sputum, should be considered as having bronchogenic carcinoma until it is unequivocally proved that there is some other reason for his symptoms.

The first diagnostic step is, of course, a roentgenogram of the chest. In most cases, this simple procedure suggests the diagnosis either by indirect evidence, such as atelectasis of a lobe or lobes due to an obstructive bronchial tumor, or by the more positive evidence of an infiltrative hilar lesion or parenchymal tumor. As mentioned above, one should not be misled into assuming that a tumor is benign because it casts a well-circumscribed shadow Such a criterion has been frequently proved invalid, and decisions taken on this basis often have led to disaster All pulmonary abscesses and suppurative lesions should be considered as resulting from bronchogenic carcinoma Since Hauser and Wolpaw (17) have shown that 12 per cent of all bronchogenic carcinoma may appear, clinically and roentgenologically, as cavitary lesions resulting from central necrosis, they must, therefore, also be differentiated from cavernous pulmonary

tuberculosis. Although in rare instances the roentgenogram is negative, in general one may say that the roentgenogram shows the tumor, which may be relatively tiny, less frequently than its result, which usually predominates in the clinical picture.

In any event, the second step in the diagnostic sequence is almost always bronchoscopy, by which a positive diagnosis before operation can best be made In Graham's experience (18), a positive diagnosis could be made by bronchoscopic biopsy in about 75 per cent of cases. Holinger and Radner (19) state that in Jackson's series a diagnosis by biopsy was possible in 75 per cent of the cases of bronchial cancer, and that Kramer and Som obtained a positive tissue diagnosis in 74 per cent of the cases and Clerf in 68.5 per cent. Again, a lesion *situated in a relatively peripheral* portion of the lung, as *happens in about 25 per cent of the cases,* will be *beyond the range of vision of the bronchoscopist, so that tissue for biopsy* cannot be secured. However, certain indirect evidence, more or less characteristic of bronchogenic carcinoma, may frequently be obtained on bronchoscopy. Thus, broadening of the carina and fixation, distortion, or compression of the bronchus suggest the presence of cancer

Bronchoscopy was performed in a recent series of 29 proved cases, by the author A positive tissue diagnosis was possible in only 14, or 48 per cent, but in 12 of the remaining a presumptive diagnosis of cancer was made. One may therefore consider that bronchoscopy either proved or pointed strongly to the diagnosis in 89 *per cent.*

Aspiration biopsy in peripherally located tumors is one of the less frequently used technics employed under special circumstances to aid in arriving at a diagnosis It has also been used, under fluoroscopic guidance, for tumors somewhat more centrally placed. Deaths from emboli have been reported, and the hazard of seeding along the needle track must not be overlooked When an effusion is present, it should be examined for tumor cells by Mandelbaum's method whereby the centrifuged sediment is fixed, sectioned, and examined histologically Such effusions usually denote extension of the tumor beyond the visceral pleura Dudgeon and Wrigley (20) have described a method for examining sputum for malignant cells which gives a high percentage of positive results if tumor cells are present, which is likely when necrosis of the tumor has occurred.

Finally, as will be discussed later, diagnosis can be established in an appreciable *number of cases only by exploratory* thoracotomy.

Treatment. *To my knowledge, there is not a single report of a 5 year cure by radiation therapy in an authenticated case of bronchogenic* cancer. *Many* radiologists, *however, believe that such* therapy is

palliative, and should be employed in some inoperable cases. In my own experience, this has not held true; in no instance has the survival time been made more bearable, the reverse, in fact, often being true.

It is now generally recognized that the ideal treatment of bronchogenic carcinoma is its surgical extirpation by total pneumonectomy. Lobectomy may be used in rare cases, but, as in cancer surgery in general, only by the sacrifice of the entire organ can one hope to achieve the greatest possible rate of cure Since the report by Graham and Singer (21) of the first successful pneumonectomy in 1933, hundreds have been performed successfully in thoracic clinics throughout the world

Unfortunately, the great majority of cases in which the diagnosis of bronchogenic cancer is made are already inoperable when first seen by the thoracic surgeon Thus, of 155 cases of primary carcinoma of the lung seen by Churchill (22) only 27 (17 per cent) were suitable for resection. Brock (23), after examining about 450 cases in 9 years, concludes that in less than 20 per cent of the cases is the prognosis favorable enough to justify exploratory thoracotomy, and that in less than half of these will the growth be found operable Actual operability in his cases at present is about 8 per cent. At the Boston City Hospital and Massachusetts Memorial Hospitals 70 cases were diagnosed from 1941 to 1943. Of these, 12 seemed operable and were explored, but pneumonectomy was possible in only 7 cases (10 per cent) Overholt (24) found 26 per cent of his cases to be operable It may be assumed, therefore, that only 10 to 25 per cent of the cases are operable when first considered for surgery Although these figures probably will improve, at present the situation is a sad reflection on our ability as physicians to recognize this relatively frequent disease in its early and favorable stages

The contraindications for pneumonectomy, which in most instances constitute the reasons for inoperability and, as a corollary, mean a late diagnosis and an advanced stage of the disease, are based on findings, which have been summarized by Graham (18) as follows:

1 The presence of bloody pleural fluid, usually denoting invasion of the visceral and parietal pleura In most cases, the presence of clear effusions is also a contraindication to operation, and the finding of tumors cells in such effusions confirms it

2 Paralysis of the corresponding half of the diaphragm, as determined by fluoroscopic examination, which usually is evidence of invasion of the phrenic nerve

3 Paralysis of the left vocal cord in cases of left-sided bronchogenic

tuberculosis. Although in rare instances the roentgenogram is negative, in general one may say that the roentgenogram shows the tumor, which may be relatively tiny, less frequently than its result, which usually predominates in the clinical picture.

In any event, the second step in the diagnostic sequence is almost always bronchoscopy, by which a positive diagnosis before operation can best be made. In Graham's experience (18), a positive diagnosis could be made by bronchoscopic biopsy in about 75 per cent of cases. Holinger and Radner (19) state that in Jackson's series a diagnosis by biopsy was possible in 75 per cent of the cases of bronchial cancer, and that Kramer and Som obtained a positive tissue diagnosis in 74 per cent of the cases and Clerf in 68.5 per cent. Again, a lesion situated in a relatively peripheral portion of the lung, as happens in about 25 per cent of the cases, will be beyond the range of vision of the bronchoscopist, so that tissue for biopsy cannot be secured. However, certain indirect evidence, more or less characteristic of bronchogenic carcinoma, may frequently be obtained on bronchoscopy. Thus, broadening of the carina and fixation, distortion, or compression of the bronchus suggest the presence of cancer.

Bronchoscopy was performed in a recent series of 29 proved cases, by the author. A positive tissue diagnosis was possible in only 14, or 48 per cent, but in 12 of the remaining a presumptive diagnosis of cancer was made. One may therefore consider that bronchoscopy either proved or pointed strongly to the diagnosis in 89 per cent.

Aspiration biopsy in peripherally located tumors is one of the less frequently used technics employed under special circumstances to aid in arriving at a diagnosis. It has also been used, under fluoroscopic guidance, for tumors somewhat more centrally placed. Deaths from emboli have been reported, and the hazard of seeding along the needle track must not be overlooked. When an effusion is present, it should be examined for tumor cells by Mandelbaum's method whereby the centrifuged sediment is fixed, sectioned, and examined histologically. Such effusions usually denote extension of the tumor beyond the visceral pleura. Dudgeon and Wrigley (20) have described a method for examining sputum for malignant cells which gives a high percentage of positive results if tumor cells are present, which is likely when necrosis of the tumor has occurred.

Finally, as will be discussed later, diagnosis can be established in an appreciable number of cases only by exploratory thoracotomy.

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carcinoma, usually denoting invasion of the left recurrent nerve as it passes under the aortic arch.

4 Severe pain in the thoracic wall or down the arm is a bad sign and generally is evidence of an involvement of intercostal nerves or of the brachial plexus The presence of a moderate amount of pain, however, should not preclude an exploratory operation.

5. *Bronchoscopic evidence of extension of the tumor into the trachea* usually contraindicates pneumonectomy, although occasionally it is possible to remove even a part of the wall of the trachea

6. The presence of distant metastases, although in exceptional cases it may prove justifiable to remove both the lung and a solitary metastasis

In the majority of cases, delay or faulty diagnosis are responsible for the conditions, as outlined above, which make operation inadvisable The patient delays seeking medical advice, considering his symptoms trivial or confusing them with a minor illness, as when he ascribes a persistent cough to the result of an acute upper respiratory infection Or he *may delay because of ignorance or fear of seeking advice.*

The physician may add to the factor of delay because he does not consider a diagnosis of carcinoma on first seeing the patient and consequently postpones roentgenologic examination, in some instances he may hesitate because of the cost of the examination A mistaken diagnosis may be *further prolonged by an erroneous interpretation of the roentgenogram*, or because the underlying malignant disease continues to masquerade as one of less serious portent

The age of the patient is important when considering operability, but so far no limit has been fixed. The patient's general condition, and particularly that of his cardiovascular apparatus, is more important than his chronologic age (Graham's oldest patient to survive was 68, another patient of 70 made a satisfactory immediate recovery, but died suddenly of coronary thrombosis one week later)

What advice one should give in the 25 per cent of cases without a positive diagnosis is a puzzling but important problem Graham (18) holds that the answer is generally fairly simple an exploratory thoracotomy should be performed without delay if there is a reasonable suspicion of carcinoma, *for this can save many lives Undoubtedly, this is the* unanimous opinion of those of us who see large numbers of these patients Too often the advice of the physician has been to wait and see if anything happens. Nothing is gained by this delay, and the usual result is another victim

An analysis of the risks involved in pneumonectomy reveals an encouraging *trend for* an operation that was first successfully performed only 12

years ago, and which technically must be considered still in its developmental stages. In 1940, Churchill (22) reported 14 postoperative deaths (67 per cent) out of 21 patients who had undergone total pneumonectomy, while only 5 out of 155 patients with proved bronchogenic carcinoma were alive, without any apparent residual disease Churchill finds these results similar to those reported by Edwards, who noted a salvage of 6 patients out of a total of 172 In Brock's (23) series of 29 operations (3 lobectomies) there were 8 operative deaths, but 4 of these occurred in patients over 60 Brock believes that pneumonectomy for bronchogenic carcinoma, if properly performed in patients under 60, should carry a mortality not much higher than 10 per cent

Graham (18) reports that in the last 25 pneumonectomies performed by him and Blades there were only 3 deaths, a mortality of 12 per cent. In a recent paper, Rienhoff (25) mentions a series of 23 cases with 3 deaths, a mortality of 13 per cent He also states that Ochsner lost only 2 patients postoperatively of his last 30, a mortality of 6 6 per cent. Such brilliant results probably could not be obtained in a larger series, but a mortality rate of 15 per cent seems a reasonable expectation

Graham further discusses the question, "Shall the thoracic surgeon offer a chance, even though a small one, to the bad-risk victim of bronchogenic carcinoma, or shall he decline to operate because of the great danger of an operative mortality?" He believes that most thoracic surgeons offer the patient a chance of recovery A mortality of 12 per cent in 25 cases is a respectable one, and should dispel the all too widespread belief that total pneumonectomy for primary cancer carries with it an enormous operative risk It should be remembered that without operation the risk is 100 per cent.

Chronic Inflammation

Although there is a wide variety of infections and infestations resulting in chronic inflammatory processes of the lungs, a broad division into tuberculous and nontuberculous lesions is best suited to a consideration of surgical therapy

Pulmonary Tuberculosis

The collapse therapy of pulmonary tuberculosis no longer requires elaborate argument in apology for its use Of proved value, it occupies a prominent place in the armamentarium of the phthisologist, and is recognized as an essential adjunct to the time-honored sanatorium regimen. Pneumothorax, open and closed pneumonolysis, and thoracoplasty have

for many years been accepted and used widely, although the indications for their use are still the subject of active discussion, and in many instances have come to be surrounded by strict limitations. In general, however, this aspect continues to be fluid. The indications for other procedures, such as phrenic interruption, extrapleural pneumothorax with and without plombage, and cavity drainage, or even their usefulness, are far from being generally accepted. Still others, such as scalenectomy and multiple intercostal neurectomy have been largely discarded and have passed into limbo. It is beyond the scope of this article to discuss in detail all the aspects of this vast problem. Those who are interested are referred to Alexander's comprehensive work on the subject (26).

Within very recent years, and with the perfecting of the technics of lobectomy and pneumonectomy, many thoracic surgeons who deal with pulmonary tuberculosis have manifested a renewed interest in the application of these procedures to its surgical treatment.

Lobectomy. During the early developmental period of the surgical treatment of phthisis, the actual removal of the portion of the lung containing tuberculous lesions was considered an attractive possibility by various clinicians. Thus, Alexander (26) states that Tuffier in 1891 resected an indurated tuberculous area in an upper lobe through an incision in the anterior second intercostal space, the patient, who was apparently cured, died seven years later of grippe Up to 1921, however, Tuffier and Jessen had collected less than a dozen cases in which tuberculous pulmonary tissue had been successfully removed, and about as many in which the operation was fatal or otherwise unsuccessful

In 1935, Freedlander (27) reported a case in which a lobectomy was performed for a persistent cavity in the right upper lobe. The patient was alive and well as reported by him (28) in May, 1944. In 1939, Jones and Dolley (29) reported 2 lobectomies and 2 pneumonectomies for pulmonary tuberculosis, all 4 patients surviving the operations. These results were considered encouraging. In 1940, Dolley and Jones (30) reviewed their previously reported cases and added 3 more In the discussion of this paper many surgeons added small series of cases, in the aggregate of which the over-all mortality was discouraging Thus, of 19 patients treated by total pneumonectomy, 8 (40 per cent) died, and of 31 treated by lobectomy 8 (26 per cent) died. In 1942, Thornton and Adams (31) collected and analyzed the reported cases of lobectomy and pneumonectomy for pulmonary tuberculosis There were 29 cases of pneumonectomy, the mortality was 45 per cent and only 41 per cent of the results were satisfactory There were 46 cases of lobectomy, with a mortality of 26 per cent and 69

per cent satisfactory results It may be assumed that the majority of the operations were performed by the tourniquet technic In these series, the most frequent complications were persistent fistula, contralateral spread, and empyema. The most frequent indications for operative procedure were tuberculoma, tuberculous bronchiectasis, bronchial stenosis, and the persistence of a cavity after thoracoplasty

It is interesting that during this period of discouragement, and at the same meeting of the American Association for Thoracic Surgery at which Dolley and Jones reviewed their results, Blades and Kent (32) reported 10 successful lobectomies for nontuberculous disease (9 cases of bronchiectasis and 1 case of mixed tumor of the bronchus) in which they employed the technic of intrahilar dissection and individual treatment of each hilar structure of the lobe This splendid contribution followed closely on the pioneer work of Rienhoff (33) on pneumonectomy for malignant disease by individual ligation, and of Crafoord (34) and Churchill and Belsey (36), the last mentioned offering new theories of segmental pneumonectomy that had hitherto been only vaguely conceived. It is reasonable to say, then, that a new era in the treatment of pulmonary disease had been entered

Up to that time surgical extirpation of the lung or one of its lobes had been accomplished by the use of a tourniquet with mass ligation of the hilar portion of the lung or lobe, as performed by Haight (37) and Graham and Singer (21) Later, after the manner of Shenstone and Janes (38), who employed a snare threaded with cord to control the hilus of the lobe, the pedicle remaining after amputation of the lobe could be made smaller and hemostasis effected by placing sutures in the presenting cut surface. Shenstone and Janes performed their lobectomies in one stage, as had Brunn (39) in 1929, when he reported 6 cases with 1 death This technic, although a milestone in the progress of the attack on the problem, was at best unsatisfactory and unsurgical, since it left masses of devitalized and necrotic tissue in the pleural cavity. Moreover, in the case of pulmonary tuberculosis, tuberculous foci were of necessity traversed during the resection of the pulmonary tissue, with the almost inevitable sequelae of tuberculous empyema or bronchopleural fistula and mixed infection empyema. Frequently the patient was left with a chronically draining chest sinus, secretions from which were often laden with tubercle bacilli. The spontaneous opening of a bronchopleural fistula during the postoperative course resulted in a high order of frequency in the bronchogenic spread of the disease in the same or the contralateral lung

As soon as the value of the individual ligation technic was proved, the

incidence of these hazards was reduced. In most cases it was no longer necessary to transect tuberculous foci or to leave masses of devitalized tissue which served as a source of infection within the pleural cavity. The hilar vessels could be individually ligated, forestalling postoperative hemorrhage, and the bronchus closed primarily and covered with pleura or buried in surrounding vital tissue, obviating to a large extent the frequently fatal complication of bronchopleural fistula. Moreover, the hilus of the tuberculous lung was found to be relatively free of the fibrosis that is present in suppurative disease, and the intrahilar dissection could be carried out with comparative ease.

In 1943, Churchill and Klopstock (40) reported 6 cases of pulmonary tuberculosis in which modern lobectomy had been performed. All the patients survived the operation and were either well or greatly improved at the time of the publication of the report. These authors make it clear that they suggest lobectomy as a highly selective measure for dealing with certain unilobar lesions. They believe that it conserves pulmonary function far more than even a seven-rib thoracoplasty. However, since lobectomy is by definition irreversible, it can be suggested as an alternate to artificial pneumothorax only when tuberculosis has produced irreversible or irreparable destruction of lung substance.

In 3 of these cases, lobectomy was performed as a definitive operation where, up to that time, thoracoplasty might have been the operation of choice In one of the patients, a 22 year old woman, tuberculin tests (1:50,000 and 1:20,000 dilutions of old tuberculin) were negative one month after operation In view of the fact that pulmonary tuberculosis is generally considered to have bilateral dissemination, even though microscopic, the implications of such a result could be significant only if many similar cases should be reported and stronger doses of tuberculin be used. Although the total eradication of all foci has been the will-o'-the-wisp pursued by phthisiologists ever since tuberculosis of the lung was recognized as an entity, its accomplishment by surgical means will in most cases probably be purely fortuitous.

At the Twenty-Fifth Annual Meeting of the American Association for Thoracic Surgery, in May, 1944, several papers were presented which evoked considerable discussion of this important aspect of the surgical treatment of pulmonary tuberculosis There were many technical issues involved that need not be reported here. Janes (41) analyzed the data in 16 lobectomies that he had performed since September, 1941 The most frequent indication was an open cavity with positive sputum The upper lobe was affected in 7 cases, the middle lobe in 1, and the lower lobe in 9

At the time of the report, 3 patients (19 per cent) had died and 13 were considered clinically well All these operations were performed by the dissection technic. Maier and Klopstock (42) reported on 16 lobectomies for pulmonary tuberculosis. There was 1 death, a mortality of 6 per cent, which occurred one month postoperatively and was due to a tuberculous spread in the contralateral lung Of the 15 living patients, 12 had a negative sputum at the time of the report These authors stressed particularly the necessity for excellent intratracheal anesthesia, meticulous operative technic, and precise localization of the lesions.

Twenty-three cases in which lobectomy was performed—with two operations in 1 case—were analyzed by Overholt and Wilson (43) in a paper read before the 1944 meeting of the American Trudeau Society There was 1 death, a mortality of 4 per cent, 5 patients (21 per cent) had ipsilateral or contralateral spreads or ipsilateral exacerbation of their disease; 21 patients of the 22 whom the authors classified as "reasonable risks" were living and the prognosis was considered good in 13 of them (62 per cent), guarded in 7 (33 per cent), and poor in 1 (5 per cent)

Although Chamberlain (44) agrees that there is a place for lobectomy in the treatment of pulmonary tuberculosis, he believes that modern selective thoracoplasty with its low mortality (2 to 5 per cent) and high rate of sputum conversion (80 per cent) should be the procedure of choice in disease of the upper lobe. He thinks that lobectomy should be performed only after failure of thoracoplasty because in his opinion, which is based on bronchospirometric studies, "primary upper lobectomy" excises only the active major focus This causes overdistention of the remaining lobes, which is probably a precursor of emphysema, and may cause reactivation of latent foci in the overdistended lobes, leaving these foci in a poor state of healing or self-protection

Maier (45) states that from previous clinical experience as well as from rather extensive respiratory physiologic studies, including bronchospirometry, which have been carried on at Bellevue Hospital over a period of years under the direction of Richards and of Cournand, it is believed that the respiratory disturbances following lobectomy for bronchiectasis are usually relatively slight There may be a difference in the problem of upper as contrasted with lower lobe lobectomy, but data on upper lobe lobectomies are insufficient to offer conclusions at this time. , Maier also points out that any study of respiratory function, done at a time when considerable pleuritic reaction remains from the operative procedure, may give a different result than studies made at a later date This does not necessarily mean that the pleuritic reaction will always subside so that the

later result would necessarily give a better result than an earlier post-operative one.

There is thus considerable difference of opinion regarding primary upper lobectomy as a definitive operation. Whereas thoracoplasty is an operation of known potential and mortality, no imposing array of statistics deals with lobectomy performed in cases in which, up to now, thoracoplasty might have been considered the operation of choice. Until such time as there is a sufficient number of cases to be of statistical significance, and until enough time—possibly five years—has elapsed to evaluate properly the results, any detailed discussion must be regarded as largely theoretic. Certainly, the use of lobectomy in well-selected cases should be continued. But the ever-present hazard of an indiscriminate use of the procedure to achieve rapidly the prestige of numbers, found all too often in the history of the surgical treatment of tuberculosis, should be guarded against with great fortitude so that the procedure will not be condemned before it has had a carefully controlled trial.

Although at the present time it seems that primary lobectomy of the upper lobe is far from being the philospher's stone in the treatment of pulmonary tuberculosis, there are other indications for lobectomy that appear to be fairly well defined. However, there is a lack of complete accord among phthisiologists and thoracic surgeons with regard to these indications. From my own experience with 17 cases (7 lobectomies and 10 pneumonectomies) and that of others (40–43), they appear to include tuberculoma, tuberculous bronchiectasis, certain tension cavities (particularly of the lower lobe), stenotic lesions of lobar bronchi, and residual cavitation when thoracoplasty has failed

Pneumonectomy. The problem of pneumonectomy in tuberculosis differs radically from that of lobectomy Churchill and Klopstock (40) state.

"Total pneumonectomy cannot be considered an alternative to collapse therapy provided that collapse therapy is applicable to the case under consideration It is both irreversible and nonselective It irrevocably and seriously limits any therapeutic procedure that may be needed for the lung of the contralateral side. Circumscribed by strict indications, total pneumonectomy in tuberculosis may be a life-saving operation when no other operation is feasible "

Since for technical reasons total pneumonectomy is in most cases performed with greater facility than lobectomy, there is undoubtedly a tendency to abandon the resection of a lobe as planned in a given case and resort to the pneumonectomy, although the original lobectomy, if persevered in,

might have been successfully completed This has obscured the issue in many cases and rendered the evaluation of results even more difficult, since the indication for pneumonectomy did not originally exist.

The most frequent indication for total pneumonectomy in tuberculosis is partial or complete stenosis of the main stem bronchus, with or without symptoms of obstruction as manifested by toxemia Thus, Lorge and Dufault (46), reporting on 3 cases from the Rutland State Sanatorium, state that in 2 the indication was stenosis of the stem bronchus and that in 1 there was wide-spread bronchial involvement with clinical evidence of repeated blockage of secretions Of the 3 patients, 1 died and in 1 a not very active lesion appeared in the contralateral lung six months later which showed evidence of clearing

Janes (41) has reported 15 total pneumonectomies. 10 were performed for stenosis, and in 7 of these there was an uncomplicated recovery. Other indications were tuberculoma, extensive infiltration of the whole lung with cavitation and hemorrhage, and cavitation of the middle lobe with infiltration to the upper and lower lobes In the total series there were 3 deaths (20 per cent), 10 patients were considered well or fairly well, and in 2 cases the outlook was unfavorable

In the series of 36 pneumonectomies reported by Overholt and Wilson (43) there were 6 deaths, a mortality of 17 per cent The authors divide their cases into "desperate risks," of which there were 11 with 5 deaths (45 per cent), and "reasonable risks," of which there were 25 with 2 deaths (8 per cent) In the total series there was a contralateral spread in 4 cases (11 per cent) In 29 of the cases pneumonectomy was performed for extensive multilobar disease that was predominantly unilateral, in 5 for uncontrolled disease following thoracoplasty, in 1 for basal tuberculosis, and in 1 for extensive disease of the upper lobe found at operation to involve the lower lobe as well There is no detailed analysis of the present status of the entire series, but of the 23 patients living who had been considered a reasonable risk the prognosis was considered good in 18 (78 per cent), guarded in 3 (13 per cent), and poor in 2 (9 per cent).

At the Massachusetts Memorial Hospitals, pneumonectomy has been performed in 10 cases of tuberculosis The indications were as follows. stenosis of the main bronchus (2 cases), extensive unilateral disease in which other measures had failed (6 cases), pneumothorax failure with an unexpansible lung (1 case), and pneumothorax failure with the cavity in the lower lobe re-opened after 3 years (1 case) There were 3 operative deaths (30 per cent), all occurring in the group with extensive unilateral disease The causes were nontuberculous pneumonia in the remaining

lung, surgical shock, and extensive tuberculous contralateral spread, respectively. Alexander (47) states:

"The choice between thoracoplasty and pneumonectomy must be based on a number of important factors. If the bronchial stenosis is so great that the patient cannot effectively evacuate the pulmonary secretions by coughing even after attempted bronchoscopic dilatation of the stricture, and consequently becomes increasingly toxic, thoracoplasty would be unduly dangerous because it probably would, at least during the period of the staged operations, further impair the effectiveness of coughing. In such cases, pneumonectomy is the operation of choice and should also be considered if thoracoplasty has already been performed and has left the patient with the symptoms just mentioned. But if there are any active tuberculous lesions in the opposite lung, or if any progressive ulcerative bronchial lesions are present, pneumonectomy is definitely contraindicated. In this event, no surgical treatment, unless possibly direct surgical drainage of a single large tuberculous cavity, could safely be used. There are very few patients who have the clear-cut indications for pneumonectomy, and, at the same time, no contraindication."

This sound opinion is probably the one held by most of the thoracic surgeons. Although the presence of bronchial stricture undoubtedly makes thoracoplasty more hazardous, Alexander, Sommer, and Ehler (48) report that 25 patients (66 per cent) in a series of 38 cases have closed cavities and negative sputum and that only 3 (8 per cent) are dead.

As is the case in lobectomy, only time and a careful follow-up will permit an accurate evaluation of the place of pneumonectomy in the treatment of pulmonary tuberculosis.

Nontuberculous Lesions

The generic term "pulmonary suppuration" connotes a chronic pulmonary parenchymal infection by a mixed flora in which anaerobic organisms frequently predominate. Such lesions may be primary, in the sense that they result from the aspiration of the proper sorts of infected material; they may progress to abscess formation or fibrosis, and result in bronchiectasis. On the other hand, they are not infrequently superimposed on pre-existing bronchiectasis and are manifestations that the infection has spread into the peribronchial zone and surrounding parenchyma of the lung—a common sequence in the natural history of bronchiectasis. The diagnosis of unresolved pneumonia is an unsatisfactory one, and in almost all cases some underlying specific cause exists. In this connection Grier (49) studied 40 cases which showed the importance of bronchography and the fact that pneumonitis secondary to bronchiectasis is often mis-

takenly diagnosed as primary atypical pneumonia. Bronchographic studies were done in cases in which resolution failed to occur in 4 to 6 weeks, but the introduction of iodized oil is contraindicated during the period of acute pneumonitis because it may aggravate the acute process Of the 40 patients, 31 had an initial diagnosis of primary atypical pneumonia, but subsequently were found to have pneumonitis around a pre-existing bronchiectasis. Grier believes that bronchographic studies should be made of all patients with pneumonia which fails to resolve in the reasonable period of 4 to 6 weeks.

Under other circumstances, an acute pulmonary abscess of the putrid type may subside, leaving a chronic abscess cavity; sooner or later, under the proper conditions, this becomes the focus for an acute exacerbation of the pneumonitis with extension into the adjacent parenchyma, or for a spilling over of the infection into previously uninvolved bronchopulmonary segments. *On a different basis but fundamentally of the same nature is* the so-called "drowned lung" resulting from mechanical obstruction of a bronchus by tumor or foreign body, with infection occurring distal to the point of obstruction.

Thus it may be seen that a multiplicity of overlapping lesions may contribute to the clinical picture of chronic pulmonary sepsis which we classify broadly as "suppurative pneumonitis" The common denominator is a spreading, and frequently destructive, or a resolving inflammation in the lung parenchyma It is with the surgical treatment of the two commonest underlying lesions, bronchiectasis and lung abscess, that this discussion concerns itself.

Bronchiectasis. It is now generally agreed that the definitive treatment of bronchiectasis is surgical, and that most patients in whom it is discovered should be considered for lobectomy or pneumonectomy, although many may, after evaluation, be denied operation for a variety of reasons

Corroboration of this statement is obtained in several recent studies, one of the best of which is presented by Perry and King (50). Basing their conclusions on a follow-up of 400 patients, these authors show that in 12 years the mortality in the non-surgically treated cases was 26 per cent, 41 per cent of these patients dying within 5 years of onset and 15 per cent living 20 years or longer after onset Of the patients who died, 78 per cent died directly from their disease. Some statistical evidence supports the view that patients who develop bronchiectasis before the age of 10 do not live beyond the age of 40. Thus, of persons with the onset in the first decade, only 9 per cent were living at the age of 40 or over, while in only 15

per cent of the 59 patients who reached the age of 40 or over was the onset in the first decade. The operative mortality in 122 lobectomies of the modern type, performed by Churchill at the Massachusetts General Hospital on 116 patients, was 3 per cent. The working and living capacity of those living patients who could be traced was considered as excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group These authors find nonsurgical treatment to be only palliative, and believe that, because of the steadily decreasing operative mortality rate, simple lobectomy may be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy—of course in two stages—is often not too great.

Bradshaw, Putney, and Clerf (51) studied 242 patients with bronchiectasis. Of these, 112 were living and 59 had died from bronchiectasis or its complications.

Riggins (52) found the mortality for 85 patients with medically treated bronchiectasis, collected during 10 years but with many of the patients observed for only 3 or 4 years, to be 14 per cent. He concludes:

> "The morbidity and mortality of untreated and medically treated bronchiectasis . . . is such that the physician who routinely advises young adults with operable bronchiectasis against surgery, is assuming a large responsibility and in all probability renders his patient a great disservice."

It should be added that children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment

Averaging the figures given by various students of the disease, Hinshaw and Schmidt (53) estimate that less than 10 per cent of patients with severe bronchiectasis obtain a satisfactory result from any form of medical treatment, and conclude that the mortality rate within 10 or 15 years after the diagnosis is made is somewhere between 30 and 50 per cent

The development of the modern technic (32) of intrahilar dissection and individual ligation has further improved lobectomy as applied to bronchiectasis Although occasionally it may not prove feasible or may even be impossible in cases of so-called "frozen hilus," because of dense fibrosis resulting from repeated exacerbations of pneumonitis, this technic materially reduces the postoperative complications of empyema and bronchopleural fistula (page 208) The advent and increasing availability of penicillin promises a further reduction in the incidence of postoperative empyema. At the Massachusetts Memorial and Boston City Hospitals

it has already been used prophylactically, in many cases both intrapleurally and intramuscularly, as part of the preoperative and postoperative routine, with gratifying results: in the past nine months we have had no case of empyema following lobectomy or pneumonectomy

Growing knowledge of the surgical anatomy of the detailed structure of the lung, refinements in bronchography, and clinical experience all have demonstrated that a lobe of the lung is actually made up of a cluster of bronchopulmonary segments. In this connection an important contribution was made by Churchill and Belsey (36) in 1939. They correctly prophesied that the bronchopulmonary segment would replace the lobe as the surgical unit of the lung Although it had been suggested by Nelson (54) in 1934 that the lungs are made up of eight lobes—two upper lobes, two middle lobes, the dorsal divisions of the lower lobes and the basal divisions of the lower lobes—it remained for these surgeons to demonstrate the actual clinical application of this anatomic configuration. They applied the principle of segmental pneumonectomy to resection of the lingula of the left upper lobe ("left middle lobe") by removing the posteromedial segment of the lingula; they also employed the technic in operations on the dorsal divisions of the lower lobes In a recent paper, Blades (55) describes a technic for other partial excisions, for example, of the basal division of the lower lobe He used it satisfactorily in 8 cases, with no deaths Such contributions are of value since they point the way to greater conservation of normal pulmonary tissue in cases in which lesions are well localized in a bronchovascular segment of the lung

No discussion of the operative treatment of a disease is complete without reference to the risks involved Churchill's excellent figures, as reported by Perry and King (50) have been mentioned. Bradshaw and O'Neill (56) report the results of surgical treatment of bronchiectasis in 76 patients whose disorder was mostly due to an unknown etiologic agent. One death occurred among the 24 patients with disease of the lower lobe and of the lower lobe and lingula, a mortality of 4 per cent Among 26 patients in whom one lobe was removed, but with disease present in other lobes, there were 4 deaths, a mortality of 15 per cent; while in 17 patients who had two or more lobes removed there were 3 deaths, a mortality of 18 per cent; 11 of these had disease in other lobes Maier (57) reports 64 cases in which pulmonary resections for bronchiectasis were performed. Lobectomy was done in 55 cases, and pneumonectomy in 9, with 1 operative death, a mortality of less than 2 per cent. Sellors *et al* (58) report on 100 cases of bronchiectasis operated on by three surgeons employing the individual ligation technic Closure of the bronchus was attempted by vari-

per cent of the 59 patients who reached the age of 40 or over was the onset in the first decade. The operative mortality in 122 lobectomies of the modern type, performed by Churchill at the Massachusetts General Hospital on 116 patients, was 3 per cent. The working and living capacity of those living patients who could be traced was considered as excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group These authors find nonsurgical treatment to be only palliative, and believe that, because of the steadily decreasing operative mortality rate, simple lobectomy may be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy—of course in two stages—is often not too great.

Bradshaw, Putney, and Clerf (51) studied 242 patients with bronchiectasis. Of these, 112 were living and 59 had died from bronchiectasis or its complications.

Riggins (52) found the mortality for 85 patients with medically treated bronchiectasis, collected during 10 years but with many of the patients observed for only 3 or 4 years, to be 14 per cent. He concludes.

"The morbidity and mortality of untreated and medically treated bronchiectasis . . is such that the physician who routinely advises young adults with operable bronchiectasis against surgery, is assuming a large responsibility and in all probability renders his patient a great disservice."

It should be added that children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment

Averaging the figures given by various students of the disease, Hinshaw and Schmidt (53) estimate that less than 10 per cent of patients with severe bronchiectasis obtain a satisfactory result from any form of medical treatment, and conclude that the mortality rate within 10 or 15 years after the diagnosis is made is somewhere between 30 and 50 per cent

The development of the modern technic (32) of intrahilar dissection and individual ligation has further improved lobectomy as applied to bronchiectasis Although occasionally it may not prove feasible or may even be impossible in cases of so-called "frozen hilus," because of dense fibrosis resulting from repeated exacerbations of pneumonitis, this technic materially reduces the postoperative complications of empyema and bronchopleural fistula (page 208) The advent and increasing availability of penicillin promises a further reduction in the incidence of postoperative empyema. At the Massachusetts Memorial and Boston City Hospitals

trabronchial lesion may be discovered, but also because the aspiration of secretions and the chemical shrinkage of the bronchial mucosa often bring about improvement in the symptoms.

Since the primary purpose of nonsurgical treatment is to bring about the maximal evacuation of secretion, cough medicines that check the cough reflex are harmful and measures that promote expectoration are beneficial. The sulfonamides, whether given by mouth or by a nebulizer, have been disappointing in chronic bronchiectasis, although in a few patients the results have been excellent.

The author recommends treatment of infection of the nasal sinuses, nose, mouth, and pharynx, this may improve the bronchiectatic symptoms. General hygienic measures, including a sanatorium type of regimen, are indicated in most cases of bronchiectasis Anemia, if present, should be treated as indicated, using transfusions if necessary. Allergic desensitization is of little value Alexander is opposed to induced pneumothorax, roentgen ray therapy, the "thirst cure," and the many operations that have been proposed or used, with poor results, before lobectomy was developed to its present state of safety and effectiveness

Kay and Meade (59) found penicillin of no permanent value in the treatment of advanced bronchiectasis, but believe it to be of considerable value in the treatment of the recurrent pneumonic episodes, as well as in decreasing the amount of sepsis and toxicity during the interval stages. It frequently decreases the cough and sputum and increases the sense of well-being; occasionally, it changes the character of the sputum However, these symptoms may recur as soon as the penicillin is discontinued. Intramuscular penicillin, usually in the dosage of 25,000 units every 3 hours, was given to 45 patients with bronchiectasis. It was continued for 1 to 2 months in most of these patients, and for as long as 3 months in 4 patients. The authors believe that the majority showed some improvement, in that the sputum decreased and the patients felt better. One-third of the patients noted no improvement, and 3 to 4 weeks after penicillin was stopped the symptoms became aggravated

Penicillin, in doses of 30,000 to 50,000 units daily at one time, was instilled into the trachea in 45 bronchiectatic patients. The majority noted improvement, some to the extent that they (the patients) felt lobectomy was not necessary However, after penicillin was discontinued, symptoms soon recurred and operative intervention was welcomed

The authors conclude that pulmonary resection should not be withheld when indicated because of the false sense of security resulting from temporary benefit.

ous methods, but no perfect method was found and bronchial fistula of varying size developed in 42 per cent of the cases. This is a considerably higher incidence of fistulas than that of most thoracic surgeons in this country. There were 8 deaths, 4 occurring within 1 month and 4 from 4 to 19 months after operation.

Kay and Meade (59) state that pulmonary resection for chronic sepsis with present-day technics, anesthesia, and chemotherapy is a safe procedure and can be recommended without hesitation. Of 100 patients on whom they performed lobectomy, there was only 1 death (an operative mortality of 1 per cent), which compares favorably with any other operative procedure.

As regards the extent of the bronchiectasis which can be determined accurately only by good bronchograms, Alexander (60) believes that *surgery is the treatment of choice for those patients whose lesions are restricted to one lobe, to the right lower and middle lobes, to the left lower lobe and lingula ("left middle" lobe), or, in some cases, to all the lobes of one lung* (total pneumonectomy), *to one lobe of each lung, or to two lobes of one lung and one lobe of the other lung (bilateral lobectomy)*

Bilateral lobectomy, in stages, has frequently been performed for bronchiectasis. *It is now considered routinely in planning the surgical program* of suitable bilateral cases Churchill (22) reports 6 cases, with 1 death. The writer has performed bilateral excision in 4 cases, *with no* death As might be expected, however, and as is borne out in Bradshaw and O'Neill's (56) figures, bilateral lobectomy is associated with considerably higher mortality, since it subjects the patient to two major operations Moreover, the postoperative period after the first lobectomy is rendered more hazardous because the patient must convalesce with disease remaining in one or more lobes.

Although the present safety of pulmonary lobectomy has solved the problem of treatment for approximately half the patients with bronchiectasis, the other half are, for a variety of reasons (particularly because of extensive bilateral lesions), not suitable for the operation Alexander (60) discusses nonsurgical methods of treatment which, if properly and faithfully carried out, can effectively alleviate the distressing symptoms of the disease in a large majority of patients, in spite of the pessimistic opinions about the value of nonsurgical treatment that have recently been expressed by a number of physicians

Postural drainage is the most valuable of the nonsurgical therapeutic measures. Every bronchiectatic patient should have at least one bronchoscopic examination, not only because some undetected important in-

that when surgery is called for, a more radical procedure than external drainage must be employed.

Although it has been estimated that adequate endobronchial drainage will occur spontaneously in about 20 to 25 per cent of cases (64), it is impossible to determine by any rule-of-thumb method exactly when a reasonable expectation of spontaneous cure ceases. This can be judged in the individual case only by careful clinical and laboratory observation, and as a result of experience in the management of the disease. A sound knowledge of the pathology of lung abscess makes it unnecessary to try this or that newly proposed remedy to know whether or not it will work.

Just when a lung abscess becomes "chronic" is a matter of opinion The time has been set arbitrarily by various authors at from 6 to 16 weeks, but it cannot, of course, be arrived at in so simple a manner. If one concedes that the ideal in the treatment of lung abscess is early external drainage—early in the sense that it is drained as soon as it has become evident that spontaneous healing will not occur (usually in 2 to 3 weeks)—one may think of chronicity in these terms. Thus an abscess that has gone past the optimal time for external drainage, and is not improving or is growing worse, may be said to be chronic Moreover, those cases in which simple drainage, though adequate, is unsuccessful because of associated bronchiectasis with persistent cavity and continued purulent discharge, are certainly chronic. And finally, clean abscess cavities giving rise to few symptoms that persist because of fibrosis and rigidity (lattice or gridiron lung) also present the problem of chronicity.

Sweet (65,66), in critical analyses of two large series of cases of lung abscess in two 5 year periods, makes several important observations on the treatment of abscesses in the chronic phases, as given above He ascribes the rise in the number of patients cured and the corresponding drop in the number who have died of the disease to improvement in the technic of the drainage operation, prompter application of surgical treatment, and particularly the utilization of lobectomy when the case was thought to be unsuitable for drainage or when drainage alone had failed to effect a cure He also points out that all other types of operation such as thoracoplasty, redrainage after failure of the drainage procedure, and plastic procedures for closure of chronic cavities were unsuccessful and were abandoned During the second 5 year period (1938 to 1942) the only surgical procedures used were drainage and lobectomy, either primary or secondary. No patient with an abscess which had existed for a year or over recovered without surgery, and very few of such long-standing cases responded to drainage alone.

Pseudobronchiectasis. In a communication emphasizing the importance of the effects of atypical pneumonia on the bronchi, and the production of pseudobronchiectasis, Blades and Dugan (61) state that 6 patients with almost identical histories have been observed at the Walter Reed Hospital. Bronchograms, following an acute illness diagnosed as atypical pneumonia, demonstrated bronchial dilatations; after one or two months the configuration of the bronchi returned to normal. The authors therefore believe that atypical pneumonia can produce temporary enlargement of the bronchi, and urge that surgical intervention be delayed in questionable cases until repeated bronchograms and the clinical features of the disease establish an unequivocal diagnosis of anatomic bronchiectasis.

Lung Abscess. During the past decade, a voluminous literature dealing with lung abscess has appeared, and is still appearing The existence of this increasing commentary on a single disease would seem to be evidence that the problems concerning it are far from settled, although of very recent years there is a trend toward unanimity of opinion as regards certain aspects, particularly the surgical treatment of acute lung abscess. Much of the credit for crystallizing and pointing the way to a rational mode of therapy of this commonplace disease should go to Dr. Harold Neuhof, of New York, and his co-workers

Surgical Treatment Briefly stated, Neuhof bases the surgical treatment of acute lung abscess on the known pathology of the lesion. all lung abscesses are peripheral with relation to the lobe in which they are located, because of this, visceroparietal pleural adhesions occur early in the course of the disease, although they are sharply localized over the abscess; if localization is precise, drainage of the abscess through the site of the adherent area may be accomplished in one stage with relative safety. In the uncommon event that the abscess is pointing on one of the interlobar fissures, a special technic is used In his latest communication, Neuhof (62) states that the operative mortality in lung abscess treated by immediate and early drainage is about 2 per cent This would seem to indicate that the prognosis of the disease is good, provided that it is recognized and treated early. But it is on the important factor of time that this program seems to go awry in most clinics Thus Churchill (63) states that in only 8 cases out of a total of 124 at the Massachusetts General Hospital during a 5 year period was the diagnosis made and the patient admitted to the hospital in less than 6 weeks. He concludes that nonoperative treatment, as a whole, is being continued far beyond the point where any reasonable chance for spontaneous cure exists. The result is irreparable damage to the lung, so

that when surgery is called for, a more radical procedure than external drainage must be employed.

Although it has been estimated that adequate endobronchial drainage will occur spontaneously in about 20 to 25 per cent of cases (64), it is impossible to determine by any rule-of-thumb method exactly when a reasonable expectation of spontaneous cure ceases. This can be judged in the individual case only by careful clinical and laboratory observation, and as a result of experience in the management of the disease. A sound knowledge of the pathology of lung abscess makes it unnecessary to try this or that newly proposed remedy to know whether or not it will work.

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In 15 cases out of 75 treated surgically a primary lobectomy was performed, and the most frequent indication was the chronicity of the case. In 10 of these 15 cases it was necessary to perform a tourniquet lobectomy, and 2 died of sepsis. All of the 5 patients who had individual ligation and separate bronchial closure were cured Primary drainage was used for 60 patients: 32 were not cured and had persistent cavities or bronchocutaneous fistulas; 11 of them were subsequently cured by secondary lobectomy or pneumonectomy without operative mortality.

In my opinion, the above well summarizes the rational surgical therapy of chronic lung abscess If there seems a reasonable chance of cure by drainage, it should be instituted; those who do not respond should have secondary pulmonary resection, lobectomy, or pneumonectomy. Cases of chronic abscess which are already of long standing (one year more or less) when first seen, and in which the chances of cure by drainage seem remote, should be treated by resection as the procedure of choice

Chemotherapy. On statistical evidence, Sweet (66) concludes that the use of sulfonamides did not materially change the results in the series he reports.

Kay and Meade (59) treated 17 patients with chronic lung abscess with penicillin, intramuscularly. The effectiveness of penicillin per se in the treatment of acute lung abscess could not be determined from their studies, since only patients who had not responded successfully to previous penicillin therapy were transferred to them for surgical treatment The toxicity in 4 patients demanded immediate drainage The others were again given a trial of penicillin therapy, as a group they showed some decrease in toxicity, with a concomittant decrease in the pulse, fever, cough, and sputum Roentgenologically, some decrease in the surrounding pneumonitis was occasionally seen. Only 1 patient was cured completely; previously he had not responded to sulfadiazine therapy In a second patient the abscess healed almost completely, only to recur On the whole, there was general symptomatic improvement, but symptoms recurred as soon as therapy was discontinued Two patients had acute exacerbations while being treated Eventually, surgical drainage was employed in all except 1 of these cases

The effectiveness of penicillin in the treatment of chronic lung abscess depends largely on the underlying pathologic changes in the lungs The mechanical factors of tissue destruction, necrosis, and gangrene, as well as the adequacy of bronchial drainage, must be considered, and the identity of the causative organisms, their virulence, and whether or not they are sensitive to penicillin, must be known These factors determine the clinical

course of such infections It is known that acute lung abscesses with adequate bronchial or bronchoscopic drainage may heal spontaneously. More will respond to sulfonamide and penicillin therapy. However, after a reasonable time has elapsed without healing, further medication with these agents should be supplemented by surgical drainage. There should be no competition of methods in the treatment of lung abscess; one treatment should be an adjunct to the other. Even if penicillin does nothing more than to prepare the patient better for operation and lessen the postoperative complications, it should be employed.

In my own experience, the tendency which must be guarded against is to persist in the use of penicillin after it becomes apparent that no further benefits are to be derived from its use in a given case of abscess While the toxemia may be reduced, fibrosis may progress to such a degree that it becomes mechanically impossible for the residual abscess to heal even when adequate external drainage is eventually established However, penicillin should be used to supplement surgical therapy when it is obvious the first time the patient is seen that surgical interference is inevitable, provided the organisms are not "penicillin fast" and are of a type which will yield to penicillin.

The inhalation of nebulized chemotherapeutic solutions such as penicillin aerosol in the treatment of lung abscess is being used in various clinics. Barach *et al* (67) recently have reported on its effect in 20 patients with bronchial and pulmonary infection Since penicillin even in extremely high dilutions is known to be bacteriostatic, inhibiting the growth of hemolytic streptococci in a dilution as low as 0 01 microgram per cubic centimeter, the potential value of inhaling a penicillin aerosol was considered likely In this series, the predominating organisms in the sputum culture were consistently absent 24 hours after discontinuance of treatment, but the number of patients is too small to be of significance The chronic abscesses were unchanged, and the improvement in three relatively early abscesses was not conclusive It is therefore still highly questionable whether the inhalation of penicillin aerosol has any advantages over intramuscular administration of the drug

Although difficult to evaluate, there is some clinical evidence to suggest that oxygen in high concentration—administered by a suitable mask—is useful in combating the anaerobes constantly present in putrid abscesses We have had only a limited experience with this method in conjunction with other forms of therapy, and, although our reactions are favorable, they are based only on clinical impressions.

Complications Due to the peripheral location of lung abscesses, per-

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respond well to vigorous intrapleural penicillin therapy, with daily doses of up to 100,000 units. The empyema may be sterilized in this way, although eventual drainage has always been necessary. The patient, however, is in a much better state for the operation, which may be of a less radical type than is done for putrid empyema.

Intrapleural administration of penicillin probably will not be of value in postponing urgent surgical drainage in the extremely virulent type of putrid empyema, but the drug should be used, intramuscularly and intrapleurally, in conjunction with surgical drainage. Following this plan in 2 patients I have noted recently a gratifying postoperative course with an even more dramatic improvement than is usually the case when penicillin is not used.

Extension of the infection, either directly into the contiguous lung parenchyma from the primary abscess or by bronchogenic dissemination into the same or contralateral lung, is the commonest cause of death after drainage of a lung abscess. In many instances, this is due to the inexorable progression of a virulent infection in a host whose tissues offer inadequate resistance. In others, the difficulty stems from the impaired efficiency of the cough mechanism as a result of which the copious, infected secretions bathing the tracheobronchial tree are not expelled. If a patient is unwilling or unable to cough efficiently because of debility or postoperative pain, frequent intratracheal catheter suction or bronchoscopic aspiration of secretions may suffice to tide him over the critical period until the cough mechanism is again functioning normally. Loss of effective ciliary action by the bronchial mucosa, which normally tends to lift secretions away from the pulmonary periphery, undoubtedly contributes to stagnation of secretions and their gravitation into the alveoli.

The action of external drainage itself, in addition to the pain factor, may seriously interfere with coughing. If the pneumonotomy opening is too large, the force of the cough blast will be considerably diminished by "backfiring" through the drainage site, particularly if large bronchi communicate directly with the abscess cavity.

It is therefore of the utmost importance, both preoperatively and postoperatively, to employ all of the available measures (forced cough, postural drainage, catheter suction, and bronchoscopy) to promote evacuation of secretions and to prevent stagnation and gravitation to uninvolved portions of the lung.

Exsanguinating *hemorrhage* stands high among the causes of death in cases of lung abscess. If erosion of a large vessel occurs, death may ensue from asphyxia as a result of sudden flooding of the air passages before

foration with consequent infection of the pleural cavity by a mixed flora is a not infrequent complication. The common organisms found are the anaerobic streptococcus and the fusospirochetal group. Acting in symbiosis, they give rise to a pleuritic exudate which has been variously termed as "foul," "stinking," or "putrid" empyema. In many instances, actual perforation of the abscess cannot be demonstrated, and it may be assumed that the infection of the pleural cavity results from the rupture of microscopic subpleural abscesses, or perhaps by actual passage of the organisms across the visceral pleura via the subpleural lymphatics. This latter mechanism has been shown to be operative under similar circumstances by several workers (68,69).

Whatever the mechanism involved, when the complication of putrid empyema occurs it must be considered, under most circumstances, as an acute surgical emergency, in contradistinction to empyemas of ordinary pyogenic origin (70). This is particularly true when the perforation assumes a valve-like action, and the problem of tension pneumothorax is added to that of the infection. In these cases, only prompt decompression by surgical means can avert a catastrophe

Even if there is no pyopneumothorax, the almost immediate effect of a virulent pleural infection of this type is frequently that of profound peripheral vascular collapse, which clinically may be indistinguishable from surgical shock If the diagnosis is suspected, it can be confirmed at once by thoracentesis and the aspiration of putrid, thin pus. When such a finding is made, surgical drainage, amply wide and open, must be undertaken forthwith Strieder and Lynch (70) have shown that when prompt open drainage is established in putrid empyema, whatever its cause, the mortality drops from about the 50 per cent prevailing when less drastic measures are used to about 14 per cent

Less frequently, a relatively benign type of putrid empyema is encountered, during the formative stages of which the systemic reaction may be mild. This may take the form of an odorless serous effusion early in the course of the complication, and the routine cultures, if they are not cultured anaerobically, are reported as showing no growth Later the exudate becomes turbid and fibrinous, and exhibits the characteristic putrid odor. This type, while not the emergency described above, should also be drained according to the same technic. Misguided attempts at frequent thoracentesis in an effort to "keep the pleura dry," are to be condemned because of the high incidence of phlegmonous cellulitis of the chest wall resulting from anaerobic infections of the needle tracks.

Recently, we have found that less virulent putrid empyemas of this type

lung and the chest wall to have become vascularized. Later the thrombus involves the walls of larger veins without completely occluding them and later still the thrombus begins to break up and form emboli in the blood stream. Most commonly these will affect the intercostal veins because the distribution of the bronchial veins is relatively limited. The thrombi will then be carried to the azygos vessels, from where in most cases they will be carried to the superior vena cava and then will be caught up in the pulmonary bed without ill effect. If, however, the thrombus becomes detached when conditions favor a reversed flow in the spinal veins, then it may enter this system and be carried to the brain These conditions will be present while coughing or straining at stool, or when the patient is lying flat on his back. Having reached the brain the thrombus will become lodged at the venous end of the capillary bed and will in consequence affect a relatively larger area than arterial embolus of the same size and will also be a certain amount nearer the surface than the similar arterial embolism. When the embolus has reached this site it will be more likely to be followed by abscess formation if it is infected with anaerobic or micro-aerobic organisms "

The practical significance of this work is, as Collis suggests, that when operative interference is undertaken in cases of *chronic* thoracic suppuration, such as lung abscess, where there has been an opportunity for vascular adhesions to form between the lung and the chest wall, the intercostal veins at the operative site should be ligated and divided in order to block the pathway by which infected thrombi may reach the brain.*

* Ed. Note. — The editors can hardly accept the thesis that tumor cells reach the

death from exsanguination can occur. Hemorrhage may occur before or after operative drainage, and in the cases where it is not immediately fatal the decision as to treatment is often difficult. When it occurs before surgical drainage, primary lobectomy or pneumonectomy must be considered, notwithstanding the grave risks of complicating infections resulting from pulmonary resection when the abscess is acute. If the infection has largely burned itself out and the abscess is chronic, the risk is considerably less (page 220). It is reasonable to expect that the newer chemotherapy may further reduce the hazards of operating in the presence of acute abscess when the surgeon's hand is forced by severe hemorrhage.

When the bleeding occurs after drainage it may be temporarily controlled by packing the cavity, but at best this is unsatisfactory and uncertain, although it must be done as the primary emergency procedure. A small and readily accessible bleeding point may be satisfactorily secured by endothermic or actual cauterization, or by suture ligation. When the bleeding point is large, inaccessible, or not easily made accessible by improving the exposure, recourse again should be had to lobectomy or pneumonectomy, frequently as a lifesaving measure. Usually the bleeding can be controlled temporarily by packing; if the patient is otherwise in reasonable condition, after blood replacement by transfusion, resection can be undertaken with considerably less risk than is the case when the infection is acute.

Metastatic brain abscess occurs frequently as a complication of thoracic suppuration; in my own experience it has been uniformly and rapidly fatal. In a recent comprehensive paper, Collis (71) states that only 2 recoveries have been recorded following surgical drainage of brain abscesses secondary to thoracic disease. In his series, this cerebral complication occurred in 4.5 per cent of the cases of lung abscess and accounted for 20 per cent of the mortality from lung abscess. There is also some evidence that its incidence has risen with the increase in operative procedures in thoracic suppuration. Modifying the technic of Batson (72), who was primarily concerned with the metastasis of carcinoma of the prostate to the brain, Collis injected the intercostal veins of cadavers with radiopaque fluid and demonstrated their connections with the spinal veins along which the fluid passed to the skull.

As regards the mechanism of the production of cerebral abscesses with particular reference to the spinal veins, Collis states:

"Thrombosis starts close to the inflammatory process in the lung or pleural cavity and gradually extends from the capillaries to larger venules. In order for it to spread to the vessels of the chest wall it is necessary for the adhesions between the

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Progress in the Development of Insecticides for Prevention of Insect-Borne Diseases

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Introduction

The need for agents with which to protect man against the host of insects that interfere with his comfort and destroy his crops has always been recognized. The demonstration, less than a century ago, that certain insects are capable of transmitting disease, and the subsequent incrimination of increasing numbers of species as disease vectors, emphasized the importance of developing effective insecticides for their control. World War II re-emphasized the need for insecticides and repellents to protect troops living in the field, and stimulated entomologic researches that have provided a number of extremely valuable new agents.

This study will trace briefly the evolution of medical entomology, and will consider some of the important new insecticides and repellents developed and used for the control of the insect-borne diseases during the war. Further research dealing with all aspects of medical entomology is still necessary and should be continued

Evolution of Medical Entomology

The relatively new science of medical entomology has developed rapidly within the life span of a single generation, but the insects are geologically old, having reached a high state of development during the Paleozoic era, and they have always exerted a profound influence on human life. Fossil mosquitoes resembling such modern genera as *Culex*, *Mansonia*, and *Aedes* have been found in Tertiary deposits which were laid down long before the age of man. Moreover, the insects are the most numerous form of animal life, and more than 600,000 species have been identified, out of a total estimated at several millions Thus, man has always lived in a world well populated with insects, while some of them have been useful, others have continuously ravaged his crops, destroyed his food, and threatened his comfort and health

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It seems not unlikely that Paleolithic man, like his vermin-harassed ancestors, spent much time fending off the persistent attacks of the biting insects, and that later the Neolithic farmer not only became concerned with protecting his crops but may have begun to suspect that in some mysterious way insects were associated with his diseases. In fact, ideas connecting insects with disease existed in some of the earliest civilizations. The ancient Mesopotamians, for example, worshipped a god of destruction and pestilence named Nergal, who commanded several disease-producing spirits and was represented by the likeness of a two-winged fly. Baalzebub, the malignant "Lord of Flies," was worshipped by the Philistines as a destroyer of flies. In ancient Indian books impure air, water, and mosquitoes are listed as causes of malaria. Throughout the Christian era, especially during the eighteenth and nineteenth centuries, there has been some speculation as to a relationship between insects and disease, but there was no experimental proof of this fact until the latter half of the last century.

In 1867, Leuckart reported the development of a helminth (*Protospirura muris*) in a meal worm (*Tenebrio molitor*); two years later Melnikow saw the larval stage of the dog tapeworm (*Dipylidium caninum*) in a dog louse (*Trichodectes canis*) and Raimbert obtained anthrax bacilli from flies exposed to animal carcasses, and in 1871 Fedtschenko observed the development of the guinea worm (*Dracunculus medinensis*) in *Cyclops coronatus*. Nevertheless, none of the standard medical texts of those years even suggested the possibility that any specific disease might be carried by insects.

The first experimental demonstration of the actual transmission of a disease-producing organism by an intermediate insect host was announced in 1878, when Patrick Manson described the development cycle of *Filaria bancrofti* in a mosquito (*Culex fatigans*) and proved that this insect is a vector of filariasis. This pioneer work, the significance of which was not immediately appreciated, was the first step in the development of the important science of medical entomology. The second step followed in 1893, when Smith and Kilborne reported that the cattle tick (*Boophilus annulatus*) transmits the protozoon (*Babesia bigemina*) responsible for Texas cattle fever, or piroplasmosis. The third was made in 1896 by Colonel David Bruce, who reported that *Trypanosoma brucei*, the cause of nagana, is transmitted from big game to domestic animals through the bite of a tsetse fly (*Glossina morsitans*), thus paving the way to the incrimination by Bruce and Nabarro in 1903 of other tsetse flies as vectors of African sleeping sickness in man. The fourth great advance came from the hypothesis formulated by Patrick Manson in 1894 that malaria is trans-

TABLE I

VECTORS OF SOME IMPORTANT INSECT-BORNE DISEASES

Diseases	Vectors: *Acarina*: Ticks	*Acarina*: Larval mites (Chiggers)	*Hemiptera*: *Anoplura* Sucking lice	*Hemiptera*: *Reduviidae* Assassin bugs	*Siphonaptera*: Fleas	*Diptera*: Mosquitoes	*Diptera*: Sandflies: *Phlebotomus*	*Diptera*: Sandflies: *Culicoides*	*Diptera*: Black flies (*Simulium*)	*Diptera*: Deer flies (*Chrysops*)	*Diptera*: Tsetse flies (*Glossina*)	*Diptera*: Filth flies
Helminths												
Filariasis												
Wuchereria bancrofti						+						
Loa loa										+		
Onchocerca volvulus									+			
Acanthocheilonema perstans								+				
Mansonella ozzardi								+				
Protozoa												
Malaria						+						
African sleeping sickness											+	
Chagas' disease				+								
Leishmaniasis												
Visceral (kala-azar)							+					
Cutaneous (Oriental sore, espundia, etc)							+					
Bacteria												
Enteric fevers												M*
Plague					+							
Tularemia	+									+		

Bartonella												
Verruga peruana (Oroya fever)							+					
Spirochetes												
Yaws							....	....	....	....	....	M*
Relapsing fever												
Borrelia recurrentis type			+									
Borrelia duttoni type	+											
Rickettsiae												
Typhus (epidemic)			+									
Typhus (endemic)					+							
Trench fever			+									
Rocky Mt. spotted fever	+											
Boutonneuse fever	+											
Rhodesian tick fever	+											
São Paulo fever	+											
Tsutsugamushi disease		+										
Viruses												
Yellow fever						+						
Dengue						+						
Pappataci fever							+					
Rift Valley fever	?					?						
Louping ill	+											
Equine encephalomyelitis	+			+		+						
Epidemic encephalitis												
Type B						+						
St. Louis						+						
Poliomyelitis	...					...	...	...	...	...	...	M*?

* Mechanical transmission.

mitted by mosquitoes; this later led to the incrimination of various species of *Anopheles* as vectors by Ross, Grassi, Bignami, Bastianelli, and others. The fifth important step was the experimental confirmation by Walter Reed in Cuba of the prior claim of Carlos Finlay that yellow fever is transmitted by the mosquito, *Aëdes aegypti*.

These fundamental discoveries stimulated a widespread interest in medical entomology and led to the incrimination of many other insects and arachnids as vectors of various disease-producing agents included among the helminths, protozoa, fungi, bacteria, spirochetes, rickettsia, bartonella, and viruses.

The insects belong to the great phylum *Arthropoda* which includes thirteen classes, five of which contain forms of medical importance, namely, *Crustacea*, *Diplopoida*, *Chilopoda*, *Arachnida*, and *Insecta*. Most of the so-called "insects" recognized as transmitters of human disease are included among the flies, fleas, bugs, and lice of *Insecta* and the mites and ticks of *Arachnida*. Although the latter are not true insects, they are commonly referred to as such and will be included in this discussion. Some of the more important groups of insect vectors and the diseases which they transmit are indicated in Table I.

Search for New Insecticides during World War II

The development of medical entomology naturally led to a search for agents with which to destroy the insects that transmit disease. The leadership in this search before World War II came largely from agricultural entomologists and others who were primarily concerned with obtaining insecticides for use against the insects destroying crops and food. Many relatively effective agents were found, some of which are also of great value in the control of the vectors of human disease. For example, Paris green and oil have been used extensively as mosquito larvicides; pyrethrum, rotenone, and other substances are used to kill mosquitoes, flies, and other insects; sulfur and other materials were formerly employed to destroy itch mites; and oil of citronella was commonly used as a mosquito repellant. These agents were of great value and many of them are still in use. But none of them were adequate for the protection of large bodies of men exposed to the insect-borne diseases of the tropics under the difficult conditions imposed by war.

The need for better insecticidal agents with which to protect the health of soldiers in the field had long been recognized by medical officers of the Armed Forces, many of whom had had experience in our tropical possessions. It was natural, therefore, that when war started in 1939 and threat-

ened to involve the rest of the world, attention was again focused on this need. In 1940, The Surgeon General of the U. S. Army took steps, through the Sanitation Division of the Preventive Medicine Service, then under the direction of Col. William S. Stone, MC, to initiate a gigantic research program in the hope of developing better insecticides for military use. This search was carried on through the cooperation of many agencies, including the Quartermaster Corps and the Chemical Warfare Service, the National Research Council, the Committee on Medical Research of the O.S.R.D., the Bureau of Entomology and Plant Quarantine of the U. S. Department of Agriculture, the U. S. Navy, the U. S. Public Health Service, the U. S. Food and Drug Administration, the Rockefeller Foundation, the Gorgas Memorial Institute, and a number of other institutions and commercial companies. Many of the country's best scientists worked on the problem and the results were coordinated and analyzed by a special committee of the National Research Council, which advised the Army and Navy concerning certain of the new agents adopted for military use.

These agents included: (a) insect repellents applied to the skin as liquids or creams, or to impregnate clothing; and (b) insecticides used in various ways to destroy the adult and larval forms and eggs of certain disease-transmitting insects.

Insect Repellents

Insect repellents are of great value for the protection of individuals necessarily exposed to certain biting insects under conditions which render the use of other methods of control difficult or impossible. Frequently, they afford the only means available for protecting troops on the march or under combat conditions, or for the protection of explorers, sportsmen, and others similarly exposed. In temporary or permanent camps where bed nets, screens, or other preventive measures are employed, these should be supplemented, when indicated, by the use of repellents during periods of outdoor exposure, as, for example, by troops on scout or guard duty, while attending outdoor theaters, or on maneuvers.

Repellents Adopted by the Army. From the large numbers of chemical agents tested as repellents, three were adopted for use in the Army. These three chemicals were: dimethyl phthalate, Rutgers 612 (2-ethyl-1,3-hexanediol), and indalone (5,5-dimethyl-γ-dihydropyrone-1-carboxylic acid, *n*-butyl ester). After laboratory and field tests had shown that these chemicals vary in their effectiveness against different species of insects, a mixture containing 6 parts of dimethyl phthalate and 2 parts each of

Rutgers 612 and indalone was adopted as the standard Army insect repellent. This standard repellent is supplied in 2 ounce bottles by the Quartermaster General and issued to troops in accordance with the estimated requirements for different geographic locations and seasons. It affords protection against mosquitoes, biting flies, fleas, mites, and partial protection against ticks for 1 to 8 hours, depending on the species and other factors.

Methods of Use. These repellents may be used either by direct application to exposed skin surfaces or for the impregnation of clothing

Use on Skin. The repellent may be applied to the skin by shaking a few drops into one hand, rubbing the hands together, and then smearing it in a thin layer over the hands, wrists, face, neck, and ears (Fig. 1). It should be uniformly distributed over the area to be protected, taking care to avoid the mouth and eyes in which it causes irritation and stinging As each of the three repellents dissolves paints, varnishes, and many plastics, it's contact with plastic watch crystals, fountain pens, or similar materials should also be avoided When used on the skin, the repellent affords protection from most biting insects for varying periods, depending on such factors as amount applied, species of insects concerned, relative humidity, amount of perspiration, and amount of rubbing to which the skin is exposed. In the Army, the standard repellent has been used on the skin most commonly for protection against mosquitoes, but it is also relatively effective against many other biting insects

Impregnation of Clothing. As a rule, insect repellents used for the impregnation of clothing and various other articles, including bed nets, remain effective for longer periods of time than when applied to the skin. To impregnate clothing, the undiluted repellent can be applied either by hand or by sprayers, or the clothing can be soaked in solutions or emulsions of the chemicals indicated. In addition to the repellent action of dimethyl phthalate against mosquitoes and other insects this chemical, when used to impregnate clothing, exerts a toxic or lethal action against larval mites (chiggers).

Hand application requires more time but affords fairly good protection For protection against flying insects, including mosquitoes and flies,

is likely to be stretched tight, rendering it easy for insects to bite through it. The repellent may also be applied to form a barrier against crawling insects (chiggers, ticks, fleas) as follows: Draw the mouth of the bottle along the cloth, applying a thin, half-inch wide layer along all openings of the uniform: inside the neck, fly, and cuffs of shirt; waist, fly, and cuffs of

trousers; socks above shoes, and all edges of leggings. New clothing may be treated in this manner several days before it is worn and one application is effective against mites until the uniform is normallly changed for laundering.

Sprayer application is more satisfactory For individuals or small groups, the ordinary hand sprayer may be used, but for large groups it is advantageous to use knapsack sprayers or paint spray guns. A rather wet type of spray is preferable to one which is delivered in small droplets or as a fog. The wet spray can be applied to clothing while it is being worn if care is taken to protect the wearer's eyes The fog-type spray is more apt to be blown away, or to get into the eyes or lungs of the operator and cause irritation, and therefore is better suited for clothing which is not being worn The garments should be turned inside out and buttoned, and the openings of the sleeves and neck of the shirt and the bottoms of the trouser legs should be closed to form baglike enclosures into which the spray is released



Fig 1 Application of insect repellent to exposed parts of the body.

Application by immersion may be employed, in which the garments are dipped or soaked in solutions or emulsions of the desired chemicals Either the standard repellent or dimethyl phthalate alone, in a 20 per cent solution in alcohol or benzene, may be used in this way After dipping the clothes in the solution, they should be hung up until the solvent has evaporated. All except dimethyl phthalate can also be dissolved in light petroleum solvents, such as Stoddard solvent

Because of the lack of suitable, inexpensive solvents for dimethyl phthalate, this chemical has usually been applied as an emulsion. Various emulsifying agents will produce fairly stable emulsions of dimethyl phthalate in water Those most commonly used in the Army are soap or commercial emulsifying agents, such as Tween-80 or G-667 (manufactured by Atlas Powder Co.)

Soap emulsions of dimethyl phthalate and other agents used in impregnating clothing may be prepared in the field as follows:

> Place 10 gallons of water in an oil drum, and add 6 pounds (about 7 cakes) of G. I laundry soap which has been cut into small pieces; dissolve by boiling and then add 25 gallons of cool water. Pour 3 gallons of the soapy water into a clean can, add 7 5 quarts of dimethyl phthalate, and stir vigorously to make a creamy concentrate. Return this concentrate to the original drum of soap solution and stir to make the finished emulsion

This represents an emulsion of about 5 per cent dimethyl phthalate in a 2 per cent soap solution, and amounts to about 37 gallons, which is sufficient to impregnate approximately 100 uniforms or 33 blankets.

Tween-80 or G-667 *emulsions of dimethyl phthalate and other agents* were also used in various combinations to impregnate clothing. During the latter part of the war, the Quartermaster issued concentrated mixtures containing 9 parts of the repellent and 1 part of the emulsifying agent. These concentrates were used in the field by adding 1 part to 17 parts of unheated water, and stirring vigorously to make an emulsion containing 5 per cent of repellent Two gallons of the concentrate, emulsified in 34 gallons of water, is sufficient for the treatment of about 100 uniforms or 33 blankets. The emulsion must be prepared just before use. The clothing, including cap, shirt, trousers, leggings, and socks, as well as blankets and mosquito bars, should be thoroughly immersed, wrung out, and hung up to dry before use.

Similar emulsions were also used in Quartermaster laundry equipment or Chemical Warfare Service impregnation equipment The clothing was placed in a rinsing machine until saturated with the emulsion and then dried in an extractor to the desired degree of wetness after which it was dried in the usual manner

Impregnated clothing was used mainly to protect soldiers from the larval mites that transmit scrub typhus, dimethyl phthalate has only a slight repellent action against these mites, but it is an effective miticide Dibutyl phthalate and benzyl benzoate, which also lack repellent action but are good miticides, were used too

Effectiveness against Mosquitoes, Sandflies, *Biting Midges*, and Flies. Mosquitoes of the important disease-transmitting species, which are included in the genera *Anopheles*, *Aedes* and *Culex*, differ markedly in their sensitivity to repellents. The standard Army repellent (6–2–2 mixture), when used on the skin, is effective for periods of only 2 to 5 hours, depending on the species concerned, when applied to clothing, however, its action

may last for several days. Sandflies of the genus *Phlebotomus* are similarly affected; against certain species, the repellent action on the skin may last as long as 7 to 8 hours. The biting midges, sometimes erroneously called sandflies, including "punkies" and "no see ums" of the genus *Culicoides*, and related types, may be repelled for 3 to 4 hours; Buffalo gnats or black flies of the family *Simuliidae* from 7 to 8 hours; and stable flies or dog flies from 3 to 7 hours. There is great need for skin repellents which will have longer action, especially against anopheles mosquitoes and other insects that bite at night.

Effectiveness against Fleas. Although fleas are not kept away from the skin by the repellents, they soon leave the treated surface and do not bite The use of repellents on clothing has been recommended for troops entering flea-infested areas where plague or other flea-borne diseases are prevalent.

Effectiveness against Larval Mites and Ticks. Those of the genus *Trombicula*, including the chiggers or harvest mites, represented in the United States by *T. irritans* and the various other species that transmit scrub typhus in the Orient, can be destroyed by the standard repellent mixture, but only because of the insecticidal action of the dimethyl phthalate which it contains. Two other effective miticides are dibutyl phthalate and benzyl benzoate. Previously, dimethyl phthalate alone was used extensively by the Army for the control of the mites of scrub typhus, because of its greater effectiveness, availability, and lower cost. It has some repellent action against mites, however, it does not keep them away from treated surfaces, but actually kills them, exerting a prolonged insecticidal action. Dibutyl phthalate, although slower in its action, has the advantage that it is not so easily washed out of clothing by rain or while wading in water. Toward the end of the war, the Army used an emulsion containing equal parts of dibutyl phthalate and benzyl benzoate to impregnate the clothing of troops in regions where scrub typhus was endemic. Many tests with both cotton and wool fabrics showed that this procedure is effective and causes no irritation of the skin Troops or individuals exposed in badly infested regions should use both the skin repellent and impregnated clothing

Ticks in the larval and nymph stages may be kept from biting by similar methods However, adult ticks are more resistant and the protection against them is less satisfactory

The insect repellents mentioned above were of value in the control of insect-borne diseases during the war It should be emphasized, however, that they were never considered entirely satisfactory and that they failed

to meet military requirements for an ideal repellent. One important defect is their relatively short period of activity Obviously, there is need for an agent which after a single application will repel anopheline mosquitoes or other biting insects throughout the entire night. It would also be advantageous to have a repellent which, after application to a small area on clothing, would repel insects at a distance and prevent them from approaching the human body

The search for better repellents is being continued, and it is hoped that more effective agents will be found to replace those which have been so useful in protecting American troops during the war

Insecticides

The wartime research program not only produced basic data on the repellents already mentioned but it made available to the Armed Forces fundamental information which led to the adoption of a number of effective "insecticidal" agents and procedures At the time of the prewar mobilization, the Army was using such well-known insecticides as pyrethrum, rotenone, sodium fluoride, Paris green, sulfur, and other chemicals in various ways for the control of insects in military garrisons. However, the program for the wartime control of insect-borne diseases, especially typhus and malaria, in overseas theaters was enormously strengthened by the adoption of a number of new agents or methods These include. (*1*) methyl bromide gas used as a fumigant for delousing clothing and military equipment, (*2*) a louse powder containing pyrethrum, known as MYL, which was used until it was replaced by DDT powder to delouse the individual soldier, (*3*) dimethyl phthalate, dibutyl phthalate, and later (*4*) benzyl benzoate, which were used to impregnate clothing and protect troops against larval mites, (*5*) the aerosol pyrethrum bomb spray used to kill adult mosquitoes, and most important of all (*6*) DDT, which was used in various ways for the destruction of lice, mosquitoes, flies, and many other insects

Methyl Bromide. Early in the war, the Army recognized the need for a more convenient method of delousing clothing and military equipment in the field, one which would be more suited to modern mechanized warfare and the rapid movement of troops than the heavy steam disinfestation chambers which were used in World War I When it was reported that methyl bromide, a liquid which vaporizes rapidly upon release from a container and which had previously been used to disinfest grain, could also be used to destroy lice and their eggs without injury to clothing or equip-

ment, a light, portable gas chamber was adopted (in June 1942) and used successfully by the Army during the early part of the war

Later, a gasproof bag was developed for use with methyl bromide in delousing the clothing and equipment of the individual soldier (Fig 2) Glass ampules, each containing 20 cc. of methyl bromide, were issued for use in these bags The method is as follows:

The materials to be deloused are placed in the bag, a 20 cc ampule of methyl bromide is inserted in a small pocket inside the bag, the bag is closed and the ampule broken by striking with a stick to release the gas The time required for delousing varies with the temperature, being 45 minutes at 60 F. or above and 2 25 hours at temperatures below 30 F. On removal from the bag, the clothes are shaken to get rid of gas, and the person doing this should stand upwind so that the fumes will be blown away from him



Fig 2 Bag of rubberized fabric used for methyl bromide fumigation in the field

In December, 1942, the Army drew up plans for large permanent methyl bromide delousing plants in all ports of embarkation, and installed and used them for delousing the clothing of military personnel returning from overseas They consisted of concrete gas chambers in buildings equipped with special ventilating systems, compressed air spraying equipment, and shower baths Later, large steel fumigation chambers were developed and installed in some of the ports The delousing procedure consisted of treating the soldiers' clothing and equipment in the gas chambers while the men bathed and were treated with a delousing spray to kill lice or eggs attached to the body This method is effective, but it does not afford any residual protection and the soldier can be reinfested within a short time

For such chambers with a capacity of about 300 cubic feet, 3 pounds of methyl bromide are required if the temperature is 60 F or above, or 4 pounds at lower temperature, and the exposure time is about 30 minutes

to meet military requirements for an ideal repellent. One important defect is their relatively short period of activity. Obviously, there is need for an agent which after a single application will repel anopheline mosquitoes or other biting insects *throughout the entire night. It would also be advantageous* to have a repellent which, after application to a small area on clothing, would repel insects at a distance and prevent them from approaching the human body.

The search for better repellents is being continued, and it is hoped that more effective agents will be found to replace those which have been so useful in protecting American troops during the war.

Insecticides

The wartime research program not only produced basic data on the repellents already mentioned but it made available to the Armed Forces fundamental information which led to the adoption of a number of effective "insecticidal" agents and procedures. At the time of the prewar mobilization, the Army was using such well-known insecticides as pyrethrum, rotenone, sodium fluoride, Paris green, sulfur, and other chemicals in various ways for the control of insects in military garrisons However, the program for the wartime control of insect-borne diseases, especially typhus and malaria, in overseas theaters was enormously strengthened by the adoption of a number of new agents or methods These include. (*1*) methyl bromide gas used as a fumigant for delousing clothing and military equipment, (*2*) a louse powder containing pyrethrum, known as MYL, which was used until it was replaced by DDT powder to delouse the individual soldier, (*3*) dimethyl phthalate, dibutyl phthalate, and later (*4*) benzyl benzoate, which were used to impregnate clothing and protect troops against larval mites, (*5*) *the aerosol pyrethrum bomb spray used to kill* adult mosquitoes, and most important of all (*6*) DDT, which was used in various ways for the destruction of lice, mosquitoes, flies, and many other insects

Methyl Bromide. Early in the war, the Army recognized the need for a more convenient method of delousing clothing and military equipment in the field, one which would be more *suited to modern mechanized* warfare and the rapid movement of troops than the heavy steam disinfestation chambers which were used in World War I When it was reported that methyl bromide, a liquid which vaporizes rapidly upon release from a container and which had previously been used to disinfest grain, could also be used to destroy lice and their eggs without injury to clothing or equip-

luted with water to make a 2.5 to 5 per cent emulsion with which the clothes are treated.

Benzyl benzoate has also been used as an emulsion in water, for the treatment of scabies. It is applied with a swab or paint brush or spray gun to cover all parts of the body from the neck down The patient is not allowed to bathe and the material is applied again 24 hours later. If desired, a third treatment may be given the next day. It is reported that this procedure cures 90 per cent of cases and is superior to treatment with sulfur ointment. Benzyl benzoate has no disagreeable odor and does not soil clothing; moreover, bathing facilities and the disinfestation of clothing are not so essential About 10 per cent of patients so treated may develop a moderate and transitory dermatitis of the genitalia

The Aerosol Pyrethrum Bomb. At the beginning of the war the Armed Services were applying insecticidal sprays by the simple spray gun methods which had been in use for more than two decades. However, the need for better methods had long been recognized, and a procedure was developed whereby insecticides dissolved in liquid gas under pressure can be discharged as aerosols which remain suspended in the air for several hours Freon-12 (dichlorodifluoromethane) which is commonly used for refrigeration, was selected as a suitable gas for this purpose It is nontoxic to man, is noninflammable, has a convenient pressure, a low peak of vaporization, and a low surface tension

A small hand dispenser suitable for use by the Army was developed These dispensers, commonly called "mosquito bombs," are small metal cylinders holding 1 pound each of the gas-insecticide mixture. At first this mixture consisted of 93 per cent Freon-12, 5 per cent pyrethrum extract (containing 20 per cent pyrethrins), and 2 per cent sesame oil Because of a critical shortage of pyrethrum, it was necessary later to decrease the pyrethrum content to 2 per cent, which so reduced the effectiveness of the spray against flies that the bombs were issued only for use against mosquitoes They were sent mainly to overseas theaters, where malaria was a serious problem

In November, 1944, the Army adopted a new formula for the insecticidal aerosol bomb which includes DDT, and is as follows

Ingredient	Per cent
Pyrethrum extract (20%)	2
DDT	3
Hydrocarbon oil	5
Cyclohexanone	5
Freon-12	85

Since methyl bromide is toxic to man in concentrations of 30 parts or more per million, a special ventilation system is required to remove the fumes which are liberated when clothes are removed from the chamber

Methyl bromide fumigation has many advantages over the older delousing methods, but it was not considered ideal for military use in the field The search was therefore continued for even simpler methods which would protect the individual for some time against reinfestation. The development of the "MYL" louse powder and later of the DDT louse powder fulfilled this need, so that eventually the field use of methyl bromide fumigation was practically abandoned, being retained only at ports of embarkation and debarkation.

MYL Louse Powder. By February, 1942, a powder had been developed which consisted of 25 per cent derris root, containing 4 8 per cent rotenone, mixed with talcum. Improvements were made in March and August and before the end of 1942 the so-called MYL powder was perfected and adopted for issue to the Army by the Quartermaster General in 2 ounce shaker-top cans. Its formula is:

Ingredient	Per cent
Pyrethrum (20% extract)	1
Dupont In 930 (*N*-isobutylundecylenamide)	2
Phenol-S (nonoxidizing agent)	1
2,4-Dinitroanisole (an ovicide)	2
Prophyllite	94

This powder not only killed all lice on the body at the time of application, but also had a residual action lasting for about a week It was considered ideal for military use and a highly effective weapon for the prevention of epidemic louse-borne typhus Its use in the Army was later discontinued only because the DDT louse powder subsequently developed affords an even longer period of effective residual action.

Dimethyl Phthalate. Dimethyl phthalate is not only repellent to mosquitoes and other insects but it exerts a true toxic action against larval mites and to some extent against ticks It has been used extensively for the impregnation of clothing and equipment in order to protect troops against the larval mites of scrub typhus in the Pacific and in the India-Burma Theater Dibutyl phthalate which has also been used for this purpose has the advantage that it does not wash out of clothing so easily.

Benzyl Benzoate. Benzyl benzoate is used as an emulsion for the impregnation of clothing to protect against the larval mites which transmit scrub typhus A concentrated stock emulsion consisting of 90 per cent benzyl benzoate and 10 per cent of an emulsifier (Tween-80 or S-667) is di-

1,1,1-trichloroethane. The symbol DDT, officially adopted by the American and British Forces, was derived from the term, dichlorodiphenyltrichloroethane, which, however, is not specific for this substance alone. Various trade names used for DDT include Gesarol and Neocid.

This chemical was first synthesized in 1874 by Ziedler in Germany, and in 1939 it was manufactured in Switzerland under the trade name Gesarol by the J. R. Geigy Company, who reported that it exerted an insecticidal action on the apple coddling moth and certain other agricultural insect pests A sample of Gesarol was brought to the United States during the Fall of 1942, at which time a search was being made for insecticides with which to replace the nation's decreasing supply of pyrethrum. Subsequently the great value of DDT in the control of a wide variety of insect disease vectors was proved beyond doubt This fortunate episode resulted in the development of a series of effective weapons with which to protect troops against louse-borne typhus, malaria, and many other insect-borne diseases.

Chemical and Physical Properties. DDT is a synthetic chemical resulting from the reaction between chloral or chloral hydrate and monochlorobenzene in the presence of sulfuric acid It crystallizes from the mass reaction and the sulfuric acid is removed by washing. As a rule, the commercial product contains isomers and is impure, however, pure DDT can be obtained by solution in ethyl alcohol and recrystallization.

The pure chemical is a white crystalline substance with a melting point of 107 to 108 C. The commercial product is a white or yellowish white powder with a lower melting point Present military specifications call for a setting point of 89 C or above. DDT retains its insecticidal action under field conditions even in the tropics, but it tends to agglomerate when exposed to atmospheres with high humidity

Insecticidal Preparations. *Powders and Dusts* The undiluted commercial product often lumps during shipment and is difficult to grind into a powder Before shipment, therefore, it was usually ground in a ball mill with a diluent powder such as pyrophyllite or talc. Such powders may be used as louse powders (10 per cent DDT), as flea, bedbug, and roach powders, or more rarely as anopheline larvicides

Solutions. DDT is practically insoluble in water, moderately soluble in mineral and vegetable oils, and readily soluble in certain organic solvents (see Table II) Its solubility increases at higher temperatures

The solutions used as residue-producing sprays for the control of adult mosquitoes, flies, bedbugs and other insects, or as mosquito larvicides, or for airplane spraying are most commonly prepared in petroleum oils such

This pyrethrum DDT aerosol bomb (Fig. 3) has an increased killing action against flies. It is effective against mosquitoes, houseflies, sandflies, midges, cockroaches, bedbugs, ants, spiders, and other insects, but has been issued principally for use against mosquitoes and flies. It leaves very little residue, and it is therefore not recommended as a substitute for the long acting DDT residual sprays used to treat walls and other surfaces

The 1 pound bomb contains sufficient material to provide for about 14 minutes of continuous spraying, and is sufficient to treat 150,000 cubic feet



Fig 3 Use of aerosol pyrethrum bomb containing DDT to kill insects inside building

of air space It may be used to spray any type of enclosure, including bedrooms, barracks, tents, bomb shelters, trenches, foxholes, jungle hammocks, mosquito bars, gun emplacements, aircraft, and ships. Four seconds of spraying is adequate for each 1,000 cubic feet of air space A "pup tent" requires only 3 seconds and a closed pyramidal tent only 10 seconds It is not necessary to spray the material directly on the insects as the gas expands rapidly, penetrates all parts of the space, and remains suspended for two or more hours

DDT Insecticidal Preparations

The most valuable insecticidal agent used by the Armed Forces during the war was DDT, the chemical name of which is 2,2-bis(*p*-chlorophenyl)-

an emulsifying agent such as Triton X-100 (manufactured by Rohm & Haas Co). A satisfactory 5 per cent emulsion can be prepared by adding to water the required amounts of a concentrate containing DDT, 25 per cent; Triton X-100, 10 per cent; and xylene, 65 per cent; (percentages by weight). Should the stock concentrate not be available, it can be made by dissolving the DDT in xylene and then adding the emulsifier To obtain an aqueous emulsion containing 5 per cent DDT for residual spraying, one dilutes the stock concentrate with 4 parts by volume of water. Emulsions can also be prepared by stirring a xylene solution of DDT into a 1 per cent soap solution. Emulsions can be used effectively instead of the solutions mentioned in the previous section

Suspensions of DDT. To make these, a powdered DDT–talc combination is mixed with a powdered wetting agent such as sodium lauryl sulfate, and the mixture shaken with water Another method is to add the DDT–talc dust to soapy water. Such suspensions have been used as residual sprays but more frequently they are employed as mosquito larvicides

DDT Items Provided in the Army. There are eight DDT items now procured by the Quartermaster General and issued for use in the Army.

(*1*) *Commercial DDT Powder, 100 Per Cent* (Item 51-L-120). Used in preparing dusts, suspensions, emulsions, or solutions for use as residual sprays, larvicides or airplane sprays

(*2*) *DDT Louse Powder* This consists of 10 per cent DDT mixed with 90 per cent pyrophyllite It is issued in 2 ounce cans (Item 51-I-173) for individual delousing and in bulk (Item 51-I-180) for mass delousing with hand or power dusters, or for the control of bedbugs, roaches, ants, and fleas

(*3*) *DDT Larvicide Powder* (Item 51-L-122) This consists of 10% DDT in talc for use as a mosquito larvicide after it has been diluted 1 part with 4 parts of dust to make a 2 per cent DDT mixture It may also be used undiluted as a roach powder

(*4*) *DDT Spray for Residual Effect* (Item 51-I-305) This is a 5 per cent solution of DDT in 15 per cent of solvent and 80 per cent of kerosene, and is used as a spray or paint to form a deposit on surfaces to kill flies, mosquitoes, roaches, bedbugs, and ants

(*5*) *DDT Spray* (Item 51-I-169) It consists of 1 per cent DDT and 2 5 per cent thanite in deodorized kerosene, and is used for spraying directly on insects or into the air of barracks, messhalls, or other rooms It is not used for residual effect

(*6*) *DDT Emulsion Concentrate* (Item 51-I-156). A stock solution, consisting of 25 per cent DDT, 10 per cent of an emulsifier (Triton X-100)

TABLE II

SOLUBILITY OF DDT

Solvent	Grams per 100 cc solvent at 27–30 C	Ounces (avoir) per quart solvent at 80–86 F.
Mineral oils:		
Fuel Oil No 2	10	3.4
Fuel Oil No 1	8	2 7
Kerosene (crude)	8	2.7
Kerosene (refined, odorless)	4	1 3
Vegetable oils:		
Soybean oil	14	4 7
Tung oil	12	4 0
Sesame oil	10	3 4
Cottonseed oil	9	3 0
Castor oil	7	2 4
Other solvents		
Cyclohexanone	100	33 6
Xylene	56	18 8
Acetone	50	16 8
Ether	27	9 1
Ethyl alcohol (95%)	1 5	0 5

as kerosene or fuel oils in concentrations of 5 per cent (about 7 ounces per gallon) As DDT dissolves only slowly in such oils, it should first be broken up, screened into the oil, and stirred for several hours. Solution may be hastened by heating to a temperature of about 90 F. The time required for solution can be shortened by first dissolving the DDT in a solvent such as the methylated naphthalenes, cyclohexanone, benzene, or xylene, and adding such concentrated solutions to the oil Cyclohexanone has been used to obtain a 5 per cent solution of DDT in purified kerosene and for its incorporation in the Freon aerosol bomb formula.

The residual spray, usually a 5 per cent solution in kerosene, is applied as a wet spray or painted on surfaces to form a deposit. One gallon is sufficient to cover 1,000 square feet of surface Mosquito larvicide sprays are made in 1 to 5 per cent solutions and applied at such a rate (2 to 10 quarts per acre) as to give about 0 2 pound of DDT per acre of water surface. Airplane sprays are used to control mosquitoes and, to a lesser extent, adult flies Larvae as well as adult mosquitoes are killed, but no prolonged residual effect is obtained When applied by plane, the rate is 0 2 to 0 6 pound (2 to 6 quarts of 5 per cent solution) of DDT per acre, depending on the type of terrain

Emulsions. These may be prepared by first dissolving DDT in a water-miscible solvent and then adding this concentrated solution to water with

quate amounts are ingested or when it is absorbed from oil solutions through the skin. In lower animals the symptoms include loss of appetite, hyperexcitability, convulsions, paralysis, and death. Dysfunction of the liver and kidneys may precede the nervous symptoms and at autopsy these organs may show evidence of toxic necrosis The powders and sprays adopted for use by the Army are not toxic for animals when used as recommended

Toxicity for Man. It seems probable that the toxicity of DDT for man is similar to that for lower animals; however, data on accidental poisoning in human beings is limited Wigglesworth (1945), who reported a case of DDT poisoning produced by the absorption of DDT through the skin of a laboratory worker, remarked.

"The general consensus of opinion, based on experiments with animals and observations on man, is that DDT used with discretion does not constitute a hazard to human health The case here recorded is the exception which tests the rule. Symptoms closely resembling those seen in animals developed only after a deliberate exposure to DDT far in excess of anything that would be likely to occur in nature"

Workers n manufacturing plants and individuals engaged in typhus and malaria control, who were necessarily exposed to large amounts of DDT for long periods of time, have been carefully observed Such persons have shown no symptoms of poisoning, but these observations may have no significance, in view of the precautions taken by those working with the chemical

Precautions. While the available evidence indicates that man has considerable tolerance for DDT, it should be borne in mind that this chemical is a poison and it must be used with caution and common sense Special care must be exercised to prevent the poisoning of individuals by accidental ingestion Being a white, practically odorless, tasteless powder, it may easily be mistaken and used for baking powder or flour It should, therefore never be stored with food When using DDT in any form in kitchens, messhalls, or dining rooms, all foodstuffs, cooking utensils, eating utensils, and table tops must be covered.

As dry DDT is not absorbed through the skin, the application of powders, either the pure chemical or the 10 per cent louse powder, is safe The extensive use of louse powders on millions of people for typhus control, and the observation of many individuals engaged in the manufacture of DDT, indicate that the danger of contact dermatitis is slight. However, when dissolved in oil or organic solvents, DDT is readily absorbed through the

and 65 per cent xylene, used (a) to prepare a 2 per cent DDT emulsion, 1 part concentrate in $11^1/_2$ parts water for louse-proofing clothing; or (b) as a residual spray against adult flies or mosquitoes (1 part of concentrate with 4 parts water make a 5 per cent emulsion); or (c) as a mosquito larvicide (1 part of concentrate with 24 parts of water make a 1 per cent emulsion), use 2 5 gallons per acre of area.

(7) *DDT Aerosol Spray Bomb* (Item 51-I-159) Made up of 2 per cent pyrethrum (20 per cent extract); DDT, 3 per cent; cyclohexanone, 5 per cent; hydrocarbon oil, 5 per cent; and Freon-12, 85 per cent, in a 1 pound metal dispenser or bomb. This spray is used to kill adult mosquitoes and flies, and 4 seconds of spraying are required for each 1,000 cubic feet of space.

(8) *DDT Delousing Spray* (Item 51-I-310). This is made by diluting 1 part of an emulsion concentrate, consisting of 6 per cent DDT, 68 per cent benzyl benzoate, 12 per cent benzocaine, and 14 per cent Tween-80, with 5 parts of water just before use It is employed to kill lice and eggs on hairy parts of the body, and it is also an effective scabicide.

Toxic Action of DDT on Insects. DDT exerts its insecticidal action either following external contact with the insects' legs, wings, or other parts, or after ingestion Its toxic effect appears to be exerted principally on the nervous system Even a short period of contact is sufficient to kill, but DDT does not have the immediate knockdown action of pyrethrum Within a few minutes, most insects (including mosquitoes) develop nervous symptoms, including hyperactivity, tremors, and uncoordinated movements, which are followed by a progressive paralysis and several hours later by death

Its effect on anopheles mosquito larvae appears to be similar to that on adults They develop nervous symptoms manifested by active erratic swimming along the surface of the water, and occasional severe tremors followed by paralysis and death

As DDT kills many kinds of insects, including some that are beneficial, it must be applied intelligently It is of special value because it retains its insecticidal effectiveness for long periods of time For example, the dusting of a soldier's clothing with DDT louse powder on one occasion is sufficient to keep him free of lice for several weeks unless the chemical is removed by washing, likewise one application of a 5 per cent residual spray to a wall protected against the weather is sufficient to kill all mosquitoes or flies that light thereon for periods of several months

Toxicity for Animals. The toxicity studies made with laboratory animals indicate that the chemical is poisonous to mammals when ade-

Louse-Borne Diseases

The important louse-borne diseases of man include: (*1*) epidemic typhus fever, caused by *Rickettsia prowazeki;* (*2*) trench fever, believed to be caused by *R. quintana,* and (*3*) relapsing fever, caused by *Borrelia recurrentis.* All three of these diseases have occurred in previous wars and epidemic typhus is notorious as an ancient military scourge.

Epidemic Typhus. Because of its past reputation, epidemic, louse-borne typhus was one of the diseases most feared at the beginning of World War II and the Army made extensive plans to combat it This program was spearheaded by the United States of America Typhus Commission, a joint Army, Navy, and Public Health Service wartime organization. The Army's program was based on two main procedures: (*1*) the immunization with a concentrated Cox-type typhus vaccine of all troops sent to regions where they might be exposed to typhus; and (*2*) the development and adoption of improved methods for delousing troops and typhus-infected civilians.

The delousing procedures employed at different periods of the war included: methyl bromide fumigation, the use of MYL louse powder, and later, the use of DDT louse powder.

Methyl bromide fumigation was recommended by The Surgeon General of the U S. Army in June, 1942 for delousing clothing and military equipment. For troops in the field it was used in light, portable, knock-down gas chambers and individual gas bags. Such procedures are highly effective and were much more suitable to modern mechanized warfare than the cumbersome steam delousing methods used in World War I. In addition, large permanent chambers for the use of methyl bromide gas were constructed at ports of embarkation to delouse military personnel and prisoners of war transported from abroad and thus prevent the introduction of lice and louse-borne diseases into the United States. At such stations, special delousing units were established where men bathed in hot water and were treated with delousing sprays, while their clothing and equipment were being disinfested in the gas chambers The latter method of mass delousing was continued throughout the war, but louse powders, as they became available, gradually replaced methyl bromide for delousing clothing in the field.

The MYL louse powder was recommended for adoption in August, 1942. This powder represented a significant advance for field use because of the simplicity of its application and its residual action. When dusted on the underwear, it kills all lice and louse eggs present and remains effective against reinfestation for approximately 1 week It was issued to the soldier in a 2 ounce shaker-top can and applied individually by shaking it on the

skin and care must be exercised to prevent contamination and prolonged contact with oil solutions. In large-scale control operations, contamination of garments and skin may be avoided by the use of coveralls and solvent-resistant rubber gloves If accidental contamination does occur, individuals should change their clothes and wash thoroughly with soap and water. The temporary inhalation of small amounts of powders or sprays during their normal application apparently produces no toxic effects However, operators engaged in large operations should use suitable respirators, wear protective clothing, and take other precautions.

It is safe to inhale the small amounts of DDT present in the air of rooms treated with the aerosol spray or the 1 per cent DDT–thanite spray; contact for short periods with DDT emulsions during the impregnation of underwear causes no irritation of the skin or other toxic symptoms After drying, impregnated underwear can be worn continuously without causing irritation

If DDT poisoning is suspected, the individual should be sent to a hospital and a complete examination should be made, including neurologic studies and repeated tests of liver and kidney functions. The treatment is symptomatic *In case the chemical is swallowed, the stomach should be* washed out with water or normal saline and 30 grams of magnesium sulfate in 250 cc. of water should be administered through a stomach tube All fats should be eliminated from the diet for several days and the patient observed for symptoms of poisoning.

Value of Insecticides in Control of Disease

The value of these new insecticidal agents and methods is shown by the excellent results obtained with them in the disease control programs of the Armed Forces As was anticipated at the beginning of the war, American soldiers, sailors, and marines were exposed to a variety of exotic anthropod-borne diseases in many parts of the world Epidemic louse-borne typhus was a hazard in Europe and in other regions, while malaria, yellow fever, dengue, trypanosomiasis, filariasis, and other diseases were a constant threat in the tropical theaters Thanks to the information gathered by the nation's wartime research program in medical entomology and the vigorous application of the new knowledge, these crippling diseases failed to hamper seriously our military progress or to delay Allied victory The following are brief indications *of the relative usefulness of these insecticidal* weapons for the control of some of the more important groups of insect-borne infections.

other parts of Europe and the rest of the world. A similar program of typhus control was put into operation among civilians of Korea and Japan.

The importance of this insecticide cannot be overemphasized. Its use has prevented a repetition of the terrible civilian typhus epidemics that followed World War I. Moreover, it has enabled the United States to protect its enormous military forces from lice and louse-borne diseases under the most trying conditions of exposure, in every region of the world.

In the entire Army during the war there were reported only 61 cases of epidemic typhus fever and 4 cases of trench fever. There were 240 cases of relapsing fever, none of which were considered as louse-borne. These insecticides have released the civilized world from the ancient fear of louse-borne diseases.

Mosquito-Borne Diseases

The important mosquito-borne diseases include (*1*) malarial fevers caused by various species of *Plasmodia*, (*2*) yellow fever, dengue fever, and the encephalitides caused by their respective viruses; and (*3*) filariasis caused by various helminths. The new repellents and insecticides afford better methods for the control of the mosquito vectors of all these diseases.

The malarial fevers caused by *P. vivax*, *P. falciparum*, less frequently by *P. malariae*, and rarely by *P. ovale*, are transmissible by a variety of species of anopheline mosquitoes which differ in their characteristic habits and geographic distribution. Thus, different mosquito control methods must be employed in various regions, depending on local conditions and the vectors concerned.

The Army's malaria control work in World War II consisted of two main programs, one carried out within the United States, and the other in the overseas theaters. The military program in this country was based largely on the intensive application of the well-known permanent anti-mosquito measures in current use in stabilized civil populations. It cost about $17,000,000 and was supplemented by a similar program in extra-military areas, conducted under the leadership of the U. S. Public Health Service, which cost about $19,000,000. As a result of this unusual malaria control work, annual hospital admission rates per 1,000 for malaria acquired by troops in this country decreased progressively, as follows:

Year	Admission rate per 1,000
1941	1.7
1942	0.6
1943	0.2
1944	0.2
1945	0.1

underwear. This powder was also used for the delousing of large groups of soldiers or civilians by blowing it either with hand or power-operated dust guns inside the clothing while it was being worn. At the time of its adoption, the MYL powder was the most valuable delousing agent available It is believed that when properly administered this powder alone should be adequate for the prevention or control of an epidemic of typhus



Fig 4 Delousing of German prisoners of war with DDT louse powder

The DDT louse powder, subsequently developed, afforded an even more potent delousing agent because when used to dust the individual and his clothing (Fig 4), its residual effect lasts for several weeks if the clothing is not washed When DDT is used as an emulsion to impregnate the clothing, it remains active and prevents reinfestation with lice even after several washings.

The wartime military experience with DDT louse powder leaves no doubt as to its value. Thousands of pounds of this powder were used to dust millions of individuals, both military and civilian, in many parts of the world It was used successfully during the civilian typhus epidemic which threatened Naples late in 1943 It was used to delouse millions of war refugees and displaced persons in Europe where it was effective in preventing the spread of typhus from foci in former German territories to

ings, tents, and other military shelters, and on nearby native huts (Fig 6); (c) as mosquito larvicides; and (d) as sprays or smokes applied by airplane.



Fig 6 Applying DDT residual spray to the inside walls of barracks building



Fig 7 Application of DDT by airplane

The development of new methods for applying DDT sprays from airplanes provided an effective means for killing both adult and larval mosquitoes

Figure 5 shows various hospital admission rates for malaria.

The Army's malaria control program for troops overseas was also well planned, but its operation was naturally more difficult, because of many factors, including the unusual hazards of exposure under field and combat conditions in tropical regions and in some instances the failure of commanders to appreciate the importance of enforcing malaria discipline. Consequently, in several locations the incidence of malaria was high at times, as for example in the Southwest Pacific during the first half of 1943

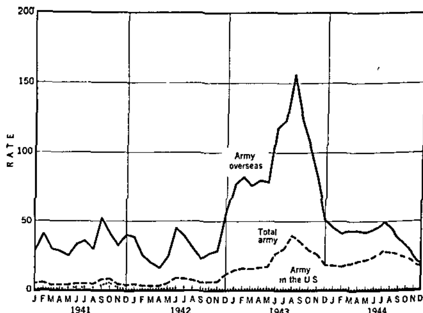


Fig 5 Malaria U S Army hospital admissions per 1,000 men per year, 1941–44

However, as the overseas mosquito control work became better organized and intensified, and the supplies of new repellents and insecticides became available, there was a remarkable decline in the disease even in those regions

The mosquito repellents were used extensively and afforded considerable protection to troops necessarily exposed to mosquitoes at night The aerosol pyrethrum bomb which became available for shipment in the autumn of 1942 was used to destroy adult mosquitoes in buildings, shelters, and airplanes When DDT became available, it was used: (*a*) as oil sprays to kill mosquitoes in the vicinity of outdoor motion picture theaters and other places of congregation; (*b*) as residual sprays on the walls of dwell-

dence of these diseases was extremely low, only 422 cases being reported in the entire Army. As had been anticipated, the troops encountered Japanese encephalitis shortly after the landing on Okinawa; but plans had been made to meet the situation and the Neurotropic Virus Commission of the Army Epidemiological Board had produced a vaccine which was used immediately. During the outbreak, which lasted from July to September, 1945, there were reported 77 cases among the natives with 19 deaths. Among military and naval personnel there were 37 cases with 2 deaths, and only about half of these patients were soldiers

Filariasis, caused by *Wuchereria bancrofti*, is a widespread tropical disease which may be transmitted by mosquitoes of many species It was of relatively little importance among American soldiers Only about 2,000 cases were reported and these were slight infections contracted by individuals stationed on tropical islands near villages where the disease was highly endemic. They could have been prevented if the prescribed antimosquito measures could have been carried out The new insecticides afford effective agents for the future control of this disease

Fly-Borne Diseases

The important fly-borne diseases fall into two main groups: (*1*) those transmitted by the biting flies, and (*2*) those spread through contamination caused by the so-called "filth" flies

The Biting Flies. The large group of biting flies which transmit disease includes various species of *Phlebotomus* (sandflies), *Culicoides* (sandflies), *Simulium* (black flies), *Chrysops* (horse flies, deer flies), and *Glossina* (tsetse flies).

Sandflies of the genus *Phlebotomus* are vectors of at least three important diseases, namely: sandfly or pappataci fever, caused by a specific virus, Oroya fever, caused by *Bartonella bacilliformis,* and leishmaniasis, caused by various species of *Leishmania* During the war, American troops were not exposed to Oroya fever and consequently there were no infections. There were 344 cases of leishmaniasis and 12,228 of sandfly fever

Sandfly fever occurred among troops in many tropical regions early in the war and its diagnosis was frequently confused with that of dengue Investigations made by Sabin (1943) and Philip, Paul, and Sabin (1944) showed that dimethyl phthalate repels *Phlebotomus papatasii* for a period of 5 to 7 hours, indicating its practical value for the protection of troops

Subsequent work by Hertig and Fairchild (1945) has shown that DDT can be used effectively against *Phlebotomus* by applying it as a residual

(Fig. 7). Airplane spraying was used during the early stages of attacks made on some of the enemy-held tropical islands, for example, Moratai and Okinawa, and it was used extensively after the capture of Manila.

Because of the chance that DDT applied to large areas by airplane might destroy beneficial insects, agricultural crops, and wild life, this procedure should not be used indiscriminately without giving careful consideration to this possibility

It is believed that of all the new procedures developed, the most valuable are the sprays which produce residues of DDT on the walls of buildings Preliminary field tests in various tropical locations indicate that this will be of material assistance in malaria control among native populations.

Yellow fever, which is transmitted by *Aëdes aegypti* and various other species of mosquitoes, was one of the diseases feared at the beginning of the war, because of the possible exposure of our troops in its endemic centers in South America or Africa, or its accidental transfer to this country by airplane. The Army control program included immunization of all military personnel passing through the regions where yellow fever is endemic, and the use of mosquito control where indicated. The repellents and insecticides used to prevent malaria may be used for yellow fever but the methods will vary according to differences in the habits of the vectors. Although large numbers of Americans passed through the endemic yellow fever areas, exposure to the disease was not great and not a single case was reported in Army personnel during the war

Dengue fever, like yellow fever, is transmitted by *Aedes aegypti*, *A. albopictus*, and probably by various other species of mosquitoes There was no vaccine against dengue during the war, although one has recently been developed and used experimentally Dengue was encountered by our troops in many tropical locations, and in certain places where mosquito control was inadequate this nonfatal but annoying disease caused local outbreaks A total of 82,392 cases were reported in the Army during the period January, 1942 to August, 1945, and the annual hospital admission rate per 1,000 was 3 7

A spectacular example of the usefulness of DDT is that of the experience on Saipan, where during August, 1942, an extensive epidemic of dengue was terminated by spraying the occupied area with oil solutions of DDT from airplanes.

Encephalitis caused by neurotropic viruses, including St Louis or Type C encephalitis and equine encephalomyelitis in this country and Japanese or Type B encephalitis which occurs in certain of the Japanese Islands, is transmissible through various species of mosquitoes The wartime inci-

less than 20 cases during the entire war However, in spite of the excellent sanitary regulations prescribed, the dysenteries and diarrheas were common in many overseas locations The annual hospital admission rates for the total Army during the war period was 22 per 1,000, being 42 for overseas troops and 9 4 among those in this country.

The importance of fly control in every major theater naturally led to an extensive search for better methods of fly destruction. DDT residual sprays were used effectively against adult flies and the 5 per cent kerosene solution or emulsions were commonly applied to surfaces where flies congregate, using 200 milligrams of DDT per square foot or 1 gallon of solution per 1,000 square feet of surface Such sprays were used in messhalls, kitchens, and latrines, on garbage racks and, if indicated, in nearby dairy installations

DDT was relatively ineffective when used as a larvicide in pit latrines or on corpses On the other hand, p-dichlorobenzene (PDB) was effective when used twice a week in airtight pit latrines A satisfactory method is to spread small crystals of PDB, about the size of rice grains, over the surface of the pit contents, using 1 pound to a 2 seat unit and 3 pounds to a 6 to 12 seat latrine. The larvicidal action is reduced by excessive water in the pit or by temperatures below 70 F

For the control of fly breeding in corpses, several insecticides were used, including sprays of sodium arsenite, *o*-dichlorobenzene, and acetylene tetrachloride, respectively British workers have reported good results with benzene solutions of benzene hexachloride (called 666).

Flea-Borne Diseases

Two important flea-borne diseases of man are plague and murine typhus Both diseases were considered potential hazards to American troops and in certain instances military personnel were located in places where both existed among the civilian population. However, during the total period of the war there were only 402 cases of murine typhus in the Army, and no plague at all.

Plague The plague control measures employed included such well-established procedures as rodent control, supplemented where indicated by the use of plague vaccine After the value of DDT for the destruction of fleas had been demonstrated, this insecticide was used to supplement further the control of plague

An example is afforded by the report of Lewis, Buehler and Young (1945) of an outbreak of plague which occurred in Dakar, Senegal, and French West Africa, from April to December, 1944 Among the local inhabitants

spray on the walls and screens of buildings and to nearby stone walls or other outside resting or breeding places.

Sandflies or gnats of the genus *Culicoides* transmit two types of filarial worms: *Acanthocheilonema perstans* and *Mansonella ozzardi*, neither of which was of importance to our troops. The use of DDT residual sprays on walls and screens will destroy adult *Culicoides*, but it is often difficult to locate their breeding places and effective methods of larval control have so far not been developed.

Black flies or buffalo gnats of the genus *Simulium* are vectors of onchocerciasis in Africa, Guatemala, and southern Mexico American troops had little or no experience with this disease during the war and no infections were reported The insects are susceptible to repellents and to the insecticidal action of DDT. However, as they rarely enter dwellings, the residual sprays will not control them. Experiments reported by Hertig and Fairchild (1945) indicate that *Simulium* larvae can be killed by adding DDT emulsions to streams in which they develop

Deer flies or gadflies of the genus *Chrysops* include species that transmit tularemia and others that transmit the filarial worm, *Loa loa* Neither disease was of importance to the Army Tsetse flies of the genus *Glossina* include *G palpalis*, *G morsitans*, and other species that transmit *Trypanosoma gambiense* and *T rhodesiense*, respectively, the causes of African trypanosomiasis in man No infections were reported in American troops during the war Although adult gadflies and tsetse flies are susceptible to DDT, their habits are such that satisfactory control methods with this chemical have not yet been developed

The Nonbiting Flies. The nonbiting flies concerned in the spread of human disease include a large group which, because of their filthy breeding and feeding habits, commonly carry on their bodies pathogenic microorganisms that may contaminate human food or drink Well-known examples are afforded by the house fly (*Musca domestica*) and the blow flies (*Calliphoridae*) These insects are believed to play an important role in the spread of certain enteric infections, such as typhoid, the dysenteries and diarrheas, and cholera However, because of the various other potential methods of transmission, it is impossible to evaluate their relative importance

During the war, the Army used vaccines against typhoid and the paratyphoid fevers A and B, so that the incidence of these diseases was extremely low—the preliminary figures being about 0 025 and 0 03, respectively, per 1,000 per year Troops in areas where cholera was a hazard were vaccinated against this disease and its incidence, also, was negligible—

The standard Army insect repellent may be used for this purpose, but dimethyl phthalate, dibutyl phthalate, and benzyl benzoate are the most effective agents now available. They can be applied to clothing by hand or by sprayer, or they can be used in solutions or in a soap emulsion for the impregnation of clothes.

Scabies. The human itch mite, *Sarcoptes scabie hominis*, has a wide distribution and many American troops developed this uncomfortable disease in the European theater. Benzyl benzoate is an effective agent for the destruction of the mite and treatment of the disease. It can be combined with DDT for use against both itch mites and lice, as follows (in per cent): benzyl benzoate, 68; DDT, 6; benzocaine, 12; and Tween-80, 14. One part of this concentrate should be diluted with 5 parts of water and the emulsion painted or sprayed over the infested parts of the body. The standard preparation now used in the Army for the treatment of scabies is a benzyl benzoate concentrate emulsion The concentrate, composed of 20 Gm triethanolamine, 80 Gm. oleic acid U. S P., and 1,000 cc. benzyl benzoate, is diluted with water to produce a 23 per cent emulsion which is applied with a paint brush or spray gun to the surface of the entire body (WD Memo 40-469, Jan. 9, 1946).

Tick-Borne Diseases

The tick-borne diseases were not common among our troops during the war There were about 60 cases of Rocky Mountain spotted fever, a few cases suspected as Q fever, and about 400 cases of relapsing fever which were thought to be tick-borne

The insecticides used for the control of mites exert some protective action against immature ticks but better methods are still needed for protection against these arthropods

Bugs of Medical Importance

The assassin bugs, including many species of the genera: *Triatoma, Rhodnius, Panstrongylus, Eratyrus, Eutriatoma*, and *Psammolestes*, occur in various parts of the world They are blood suckers and a number of species have been incriminated as transmitters of *Trypanosoma cruzi*, the cause of Chagas' disease Further experimental study will be required to determine the role of insecticides in their control

Bedbugs of the genus *Cimex*, including *C lectularius* and *C hemipterus*, are commonly found in human habitations, the former in temperate zones, the latter in the tropics Both species have been suspected as vectors of a number of human diseases, but the evidence is largely based on laboratory

there were 567 cases with 514 deaths, a mortality of 91 per cent, but no infections occurred among American soldiers or sailors. In addition to vaccination, segregation, and rat control, a vigorous antiflea program was carried out between October 24 and November 16, during which the inhabitants were dusted with 10 per cent DDT powder and the dwellings and public houses were either treated with the powder or sprayed with 5 per cent DDT in kerosene This program was followed by a marked reduction in the flea population and the outbreak soon stopped.

Murine Typhus. The value of DDT for the destruction of fleas is also indicated by the experience of the Typhus Control Unit of the U. S. Public Health Service which, under the direction of Medical Director C. R. Eskey, is using this chemical in an extensive program for the control of murine typhus in the southern United States. The report of this Unit states:

"Ten per cent DDT powder is placed in active rat runs and in small patches around the food, water, harboring places, and entrances, and in burrows where rats are travelling . . . It is also important to dust such places as cat and dog houses and chicken coops . . . . Little danger to the animals is experienced except in the case of kittens . . ."

It has been shown by Lindquist and Bushland (1945) that the addition of 0 2 per cent pyrethrins and 1 per cent *N*-isobutylundecylenamide to the 10 per cent DDT powder provides better protection against fleas, as it paralyzes the insects more quickly.

Mite-Borne Diseases

Scrub Typhus Various species of larval mites of the genus *Trombicula*, known as harvest mites or chiggers, are widely distributed throughout the world In many locations, as in the United States and Europe, they appear to be merely annoying pests; but in other parts of the world certain species transmit to man a serious infection caused by *Rickettsia orientalis* In Japan this is known as river fever or tsutsugamushi disease, in Formosa as pseudotyphus, and in the Federated Malay States as scrub typhus. American troops were exposed to this disease in the Southwest Pacific, in the Philippines, and in the India-Burma theater, but thanks to the development of effective methods for controlling the vectors, less than 7,000 cases were reported during the entire war.

The control methods used include: (*a*) clearing and burning of grass and scrub on new camp sites, (*b*) avoidance of sleeping on the ground; (*c*) avoidance of bathing and scrubbing the skin with a rough cloth after exposure; and (*d*) wearing clothes impregnated with antimite fluid (Blake and Maxcy, 1945).

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experimentation. DDT affords an effective agent for the control of bedbugs. These insects can be eradicated from dwellings and barracks by spraying a 5 per cent DDT solution in kerosene, or an emulsion, on all beds, including mattresses, springs, and bedsteads, and into the cracks and crevices in walls About 100 cc. of spray are required for a bed, and 3 gallons are sufficient to treat the beds and walls of a 74 man barracks.

Cockroaches may constitute a nuisance in military buildings, especially in messhalls and kitchens A 10 per cent DDT powder, or a 5 per cent DDT spray, is equal to or superior to undiluted sodium fluoride for the control of roaches, especially the American roach, *Periplaneta americana.*

Conclusion

It may be stated that the wartime researches in medical entomology have afforded better repellents and insecticides with which to protect troops against the insect-borne diseases and these agents will be of importance to the future improvement of civilian health, especially in the tropics. It is reassuring to know that plans are being made to continue the nation's entomologic research program, for if this is done, we can expect further advances in the control of these important diseases.

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and in the fabrication of electrically heated garments through well-integrated and extensive physiologic test and research programs of the Army, Navy, and the National Research Council.

Underwater operations consisted of salvage work on ships, clearing of harbors, and large-scale defensive and offensive submarine military measures, including "midget submarines" and divers with special breathing equipment to demolish surface ships The principal medical developments were an increased knowledge of the limits on oxygen inhalation at high pressures and the formulation of effective tables for treating compressed air illness By means of a simulated dive using helium–oxygen mixtures, man's tolerance for high barometric pressure was found to be at least 18 atmospheres (equivalent to a diving depth of 550 feet).

Selection and Training of Personnel

Aviation psychologists have convincingly demonstrated that the percentage of successes and failures in groups of men can be predicted for such tasks as pilot, bombardier, and navigator, on the basis of aptitude, personality, and interest In large-scale training programs, where the cost per individual is of the order of $25,000, a premium is placed upon the early elimination of the unfit.

Of the highly successful selection tests, the biographic inventory best illustrates the flight surgeon's replacement of intuitive methods of sorting candidates by a predictive procedure employing biographic information in a statistically exact arrangement (1). In an analysis of 8,615 records, it was found that the men who scored *A* on the inventory had a failure rate of 11 per cent, while those who scored *E* had a failure rate of 59 per cent

Several *psychomotor tests* (2)—*a two-hand coordination test previously* used in industry as a measure of proneness to accident, a discrimination–reaction-time test, and a serial action apparatus that reproduced in simplified form the mechanical adjustments involved in flying, proved useful Complementing these tests was a battery of verbal, mathematical and reasoning tests involving such factors as measures of spatial relationships and fundamental mechanical concepts The composite predictive value of these tests in eliminating failures and their cost in terms of elimination of potentially successful candidates is determined by the "cut off" level chosen (Table I).

Physical fitness tests as embodied in the Army Air Forces' test battery and the step-up test (4) and its modifications have been useful for following the progress of individuals engaged in physical training Such tests, in

Physiologic and Medical Aspects of Aviation and Deep Sea Diving*

CAPTAIN A. R. BEHNKE, (MC), USN

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Introduction

Underlying the air suprem...

defeat of ... were trained monthly

den ... units within the continental limits of the

in ... United States. The continuous hazards of combat, confinement in small working spaces, rapid changes in pressure and temperature, unaccustomed motion, noise, and vibration, and irregular sleeping and dietary schedules to which these men were subjected caused physiologic derangement and psychic traumas that called for preventive and therapeutic measures on a scale unknown in civil life. As a result of these stresses applied to healthy men there arose problems of primary concern not only to the physiologist but to the internist—problems which required an approach and analysis wholly different from that applied to ill patients.

The remarkable resistance to trauma and the ... exhibited by young healthy men ... range and ...

Yet ... development of the of b... mac... were high, protection against crash injury was inadequate, and failure of personal equipment to function properly took its toll, in brief, the machine could go too high, travel too fast, and was too complicated to be completely mastered by man. However, noteworthy progress was made along certain lines, chiefly in protecting air crews with body armor, in the fabrication of an "anti-g" suit to counteract the effects of centrifugal force, in procedures for selection and training of personnel, in the provision of oxygen at altitudes above 8,000 feet, in the increase in the oxygen ceiling by means of pressure ...

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* The ...

has been shown that there is no correlation between pulse rate response to moderate exercise and muscular endurance time. Only work, as for example on a treadmill, carried to exhaustion gives a measure of endurance Degree of motivation, the chief variable affecting endurance, can be estimated from the pulse rate immediately following exercise. Any rate less than 140 beats per minute based on a 15 second count (taken 5 to 20 seconds after exercise) indicates lack of exertion.

The importance of the age factor is shown in an impressive manner by endurance scores of men engaged in the same general activities and presumably in the same stage of training When sustained muscular work, such as that involved in step-ups or sit-ups, is carried to exhaustion, there is a linear decrease in endurance time beginning at about the age of 23

Anthropometry. The size, shape, and gross movements of the body have assumed great importance, in view of the limited space in the cockpit and other parts of aircraft Masses of data on the physical measurements of aviators have been assembled at Wright and Randolph Fields, the Army Air Forces' chief aviation research facilities. In the early part of the war, the fitting of oxygen masks was a major difficulty. The masks tended either to slip and leak, or cause severe discomfort from small pressure areas. In the first case the aviator received no benefit from the mask, and in the second he simply refused to wear it The extensive anthropometric data on shape and size of head and face, statistically analyzed, furnished a basis for the manufacture of masks of shapes and sizes to fit the majority of aviators (6)

Night Vision. Although the ability to recognize objects is no more dependent on visual acuity than ability to see through a microscope, it was still somewhat of a surprise that no special test of visual function had any high degree of predictive or even classification value for ability to see at night

A selection procedure based upon the power of dark adaptation eliminated the 1 to 5 per cent of men who were relatively night blind The remaining men could not be accurately classified due to the nemesis of all functional tests on healthy men, namely, individual variation of scores from day to day Moreover, agreement could not be reached as to what was the best test procedure The extensive and carefully performed work in this field was disappointing, and is an illustration of the difficulties attending any selection procedure involving refined psychomotor function seemingly amenable to precise measurement Because of variation in the performance of a given individual due to uncontrolled physio-

TABLE I

PERCENTAGE OF MEN ELIMINATED FROM EACH APTITUDE CLASSIFICATION (BASED ON PRESELECTION TESTS) BECAUSE OF FLYING DEFICIENCY (3)

Number of candidates 9,823, eliminated, 3,530 (35.9 per cent)

Aptitude rating	Per cent failures	Aptitude rating	Per cent failures
1	5.5	6	47.6
2	14.7	7	57.7
3	18.8	8	69.4
4	27.2	9	82.4
5	36.3		

the main, are valid only for group comparisons (Table II), or for an individual if a pattern of responses has been established

In following groups of men exposed to stress or to industrial hazards, increase of mean pulse rate value serves as a quantitative measure of cardiovascular response. Individual variability of pulse rate following exercise usually precludes high test–retest reliability, yet under carefully controlled conditions consistent results can sometimes be obtained. As with laboratory procedures, they must be carried out meticulously, and used not as absolute criteria but as helpful adjuncts in determining fitness In practice, they have not been precisely administered and too much has been read into them

TABLE II

AVERAGE PULSE RATE RESPONSE TO EXERCISE* OF 40 MEN ON 2 OCCASIONS AT INTERVALS OF 5 DAYS (5)

Sample statistics	Pulse rate, beats/min					
	Standing		5–20 sec after exercise		105–135 sec after exercise	
	June 7	June 12	June 7	June 12	June 7	June 12
Range	64–116	64–116	23–39	23–39	32–53	29–57
Mean	92	88	33	32	44.6	42
Median	92	88	33	31	43	41
I R †	80–101	80–96	30–36	28–35	41–49	35–49

* Twenty step-ups in 30 seconds on a platform 18 inches high using the same leg and timed with a metronome

† Interquartile range Tenth and thirtieth pulse rate values (25 per cent above and below median), when these values are averaged in order of increasing magnitude

Frequently, errors in interpretation arise, e g , in predicting endurance from the pulse rate following moderate exercise or postural changes It

consistent biometric data obtainable and agree to within 0 003, provided that the body weight remains constant.

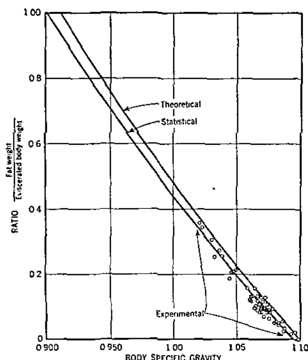


Fig 2. Ratio of fat weight to eviscerated body weight plotted against the body specific gravity for the guinea pig (8)

The specific gravity of the body varies inversely with, and is chiefly affected by, the amount of fat present (sp gr. 0 93) (Fig. 1). Thus:

$$\frac{\text{weight of fat}}{\text{total weight}} = \text{fat} \frac{1}{\text{sp gr}}$$

or

$$\text{fat (per cent of body wt)} \doteq 500\ (1\ 100 - \text{sp gr})$$

The value 1.100 is taken as the density of the lean body mass The concept that the body consists of a lean mass of constant composition, and that accumulated fat is the major component responsible for alterations in specific gravity (7) was established during the past year by Rathbun and Pace (8) The lean body mass appears to be constant not only in regard to

logic factors such as diet, rest, or ingestion of alcohol, this and other test procedures are chiefly useful for group comparisons *Until these factors* are controlled, one score will not be a reliable index of an individual's ability in the function tests.

Although no measure was evolved for *improving innate ability (retino-cortical function)* to see at night, the substitution of red light for the time-honored battle blue light provided conditions more favorable to the maintenance of dark *adaptation* (9). *Safeguarding night visual function*

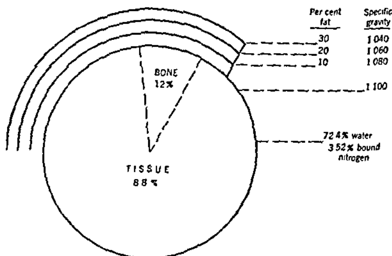


Fig 1 *Weight relationships between excess body fat and lean body mass* (40) The specific gravity values forming the basis for the diagram are: fat, 0.93, tissue, 1.060, bone, 1 50

by protecting men from exposure to bright sunlight by means of red goggles also proved to be effective Other measures to maintain night vision were administration of oxygen for all night fliers and provision of adequate diet

Body Composition. *Obesity has long been recognized as a major pre-disposing factor to decompression sickness since fat has five times the capacity of water to dissolve nitrogen, and the fat depots may therefore be regarded as potential gas reservoirs.* Accurate estimates of the fat in a given individual cannot be derived from height–weight tables, but computing body density by using the method of hydrostatic weighing based on Archimedes' principle for the computation of body volume was helpful (7). Repeated determinations of body specific gravity provide some of the most

specific gravity but also in regard to the relative content of water, bone, and various solid constituents Using adult guinea pigs of various weights, these investigators obtained the same range of values, 1.021 to 1 097, as was found for man. Aliquot fat-free samples of pulverized body tissues including bone yielded a value of 1 098 Furthermore, the inverse relationship postulated for man as existing between specific gravity and fat content was established for the guinea pig (Fig 2)

The concept that the lean body mass is of uniform composition is also supported by the findings of Pace and Rathbun that the percentages by weight of water and of combined nitrogen in the aliquot fat-free samples of pulverized tissue show remarkably little variation (Fig. 3). This concept is important in that it may greatly alter the meaning of present values of metabolic rates. Tables based on lean body mass rather than surface area would presumably show much less variability and hence be of greater predictive value Since changes in weight occur with age, the present relationship between age and metabolic rate needs thorough revision.

Effects of Compression

The theory that pressure changes in themselves, apart from disturbances in gaseous equilibriums, do not induce physiologic effects provided that the pressure is equally distributed on all parts of the body, is still to be regarded as tenable If oxygen pressure remains constant, metabolism is not affected by altitude change It is well known that blood and cerebrospinal fluid pressures are not altered by as much as a millimeter during rapid fluctuations of pressure over a range of many atmospheres Any effects on cardiorespiratory function, for example, can be attributed to change in oxygen pressure or to the effect of the altered density of the respired gas.

Pathologic Conditions of Ears, Sinuses, and Teeth

Aero-otitis Media. Such remarkable tolerance to pressure does not hold if pressure is unequally distributed over the surface of the body, e g , in fluctuating pressure boots Differential pressures of the order of 50 to 100 mm mercury (0 5 lb per sq. in.) are associated with vascular distention and pain The most common symptom associated with compression in diving or altitude descent is pain in one or both ears when the auditory tubes are obstructed. In altitude and high pressure chambers, the incidence of severe aero-otitis media during the compression phase of exposure is 6 to 15 per cent, the higher incidence occurring during the months when acute infection of the nasopharynx is highest (10) (Fig 4).

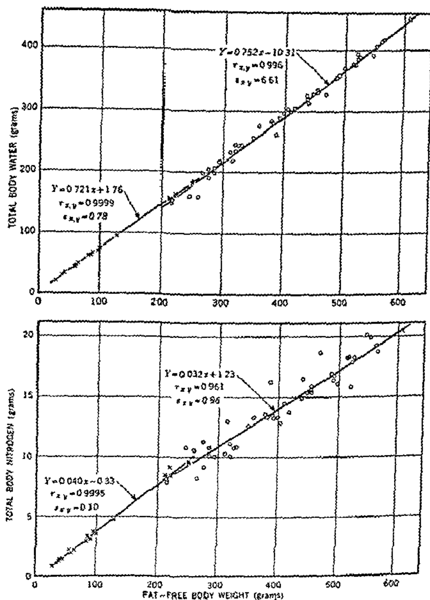


Fig 3 Upper graph represents the total body water plotted against the fat-free body weight for each animal in the series of guinea pigs (O) and for each animal in the series of rats (X) studied by Ashworth and Cowgill Lower graph represents the total body nitrogen plotted on the same basis The equations were obtained by the method of least squares (8)

The rate of compression is the most important factor governing degree of trauma. In high pressure chambers and in diving, descent can be made at a rate equivalent to 100 feet per minute (>45 lbs per sq. in.), this is comparable to descents in the low pressure chamber of 3,000 to 5,000 feet per minute *However, in commercial passenger aircraft the rate of descent* is limited to 300 feet per minute and the incidence of frank otitis media among passengers has been less than 0 5 per cent

In the treatment of aero-otitis it should be emphasized that recovery takes place spontaneously. *Special measures are contraindicated.* Infection of the middle ear is no more common following pressure trauma, provided swimming is avoided, than it is in the general population With respect to hearing following acute pressure trauma, the audiogram reflects temporarily diminished perception of sound over the whole frequency range. The rarity or absence of permanent deafness from pressure trauma is in contrast to the frequent impairment produced by gunfire.

The most promising measure to reduce the incidence of otitis media due to chronic obstruction is the application of radium to the posterior nasopharynx to bring about atrophy of obstructing lymphoid tissue (13)

Aerosinusitis. Involvement of the sinuses, usually the frontal due to blockage of the frontonasal duct, occurs in 1 to 2 per cent of exposures to compression The same type of injury to the lining membrane is produced as in the ear. The pain elicited is severe and rather sharply limited to the area involved. A mild form of pressure trauma is that brought about by the absorption of oxygen in occluded frontal sinuses during the course of acute nasopharyngeal infection which induces the familiar "vacuum" headache

Aerodontalgia. A very interesting phenomenon is the dental pain elicited during test exposure in the high pressure chamber which has recently been described as occurring in 1 to 2 per cent of aviation personnel. The etiology of this pain has not been clarified by experimental work. It seems unlikely that it is due to any other cause than differential pressure, which implies the presence of free gas either in blood vessels or extravascular pulp tissue introduced during dental treatment or in some other manner. The dental pain sharply limited to specific teeth (excluding maxillary sinusitis) indicates that the pulp is diseased (14)

Empiric data to date demonstrate the value of pressure chambers in detecting gradations of obstruction of auditory tubes and sinal openings which are undetectable by current diagnostic methods. In dentistry, diagnosis of a latent type of pulpitis can be made only by means of such a

Some degree of aero-otitis may be observed in 33 per cent of individuals exposed (11).

After or during the breathing of oxygen, aero-otitis may develop during sleep The reason for this is that the eustachian tubes rarely open during sleep and, since the oxygen is absorbed more rapidly than the nitrogen diffuses, the pressure in the middle ear may fall fast enough to cause edema, venous hyperemia, and pain as a result of "cupping."

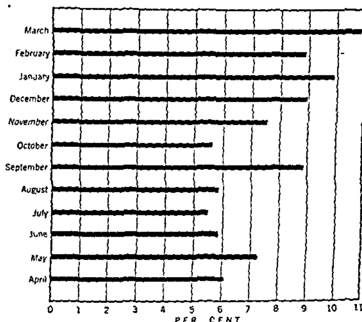


Fig 4. Monthly incidence of "ear block" in aviation cadets during altitude training at a naval base in Texas, 1942–1943 (10) · Data compiled by Lt Comdr. W E Williams, (MC), USN

The etiology of the pathologic changes observed during compression can also be ascribed to cupping action on tissues when the pressure in the middle ear is "negative" relative to tissue pressure. Vascular dilatation, rupture, and even hemorrhage may occur during elevation of barometric pressure. That pain is the result of vascular distention and is mediated through sensory fibers running in periarterial sympathetic plexuses, is an intriguing hypothesis, and is supported in part by the observed distortion of pulmonary vessels associated with gas bubbles following rapid decompression (12) which is postulated as giving rise to the substernal distress associated with "chokes."

epileptiform in character, continues to be the most remarkable phenomenon of oxygen poisoning. As in idiopathic epileptic seizures, there are no clinical signs of injury following single convulsive seizures in man, but in rats multiple daily exposures, and occasionally a severe single exposure, have been shown to produce motor disabilities associated with spastic paralysis.

Apart from the influence of increased carbon dioxide tension in the lungs and tissues and of exercise, little is known of the factors affecting and underlying the course of oxygen poisoning The extensive studies of Stadie *et al.* seem to indicate a likelihood that the explanation of the toxic action of high pressure oxygen lies in inhibitory actions on enzymes, with resultant severe disturbances of essential metabolic cellular reaction (18).

Nitrogen. The narcotic action of atmospheric nitrogen, which becomes apparent at pressures greater than 4 atmospheres (100 feet diving depth), induces psychomotor impairment and even loss of consciousness at pressures in excess of 10 atmospheres (300 feet diving depth). This phenomenon resembles in many ways the state of light anesthesia, and may be explained, at least in part, by the Myer-Overton hypothesis which relates effectiveness of anesthetics to high lipid solubility as compared with water. The substitution of helium, which has a much lower oil-water solubility ratio than nitrogen (He 1 7, N 5 3), greatly minimizes the narcotic effect at high pressures. In a recent simulated dive to 550 feet in which a helium–oxygen mixture was breathed, the diver remained in good condition throughout and subsequent to the period of the dive

Haldane has confirmed the finding that air at high pressure (8 6 atmospheres) has an intoxicating effect and that this effect can be abolished by substituting helium or hydrogen for nitrogen. Lawrence and his group have recently summarized information on the oil–water solubilities of a number of gases (19)

Role of Carbon Dioxide in Nitrogen Narcosis. Carbon dioxide probably increases the narcotic effect of nitrogen, since this effect is greatest immediately upon reaching sea bottom, at which time the carbon dioxide pressure is presumably the highest Some workers in the field believe the effect of carbon dioxide may be primary rather than secondary, but experimental data do not support this concept The action of carbon dioxide in increasing cerebral blood flow would presumably render a given pulmonary gas pressure more effective, i.e , more nitrogen would be delivered to the brain per unit of time At atmospheric pressure, carbon dioxide in closed compartments may be permitted to build up to 5 per cent over a period of 35 hours. As a result of hyperventilation, the increase in carbon dioxide pressure to 36 mm. Hg (approximately 5 per cent) in ambient air brings about a

chamber; this diagnostic aid should prove most helpful in solving the perennial problem of advisability of extracting nonvital teeth.

Pulmonary Gases

Carbon Dioxide. One immediate effect of rapid compression is an increase in alveolar carbon dioxide pressure. Conversely, during rapid decompression, carbon dioxide pressure tends to fall Prior to the establishment of equilibrium, the effect on the respiration in divers has been noted following rapid descent and in the low pressure chamber during rapid ascent. Other than the initial changes, pulmonary ventilation is the same for a given degree of activity from ground level to barometric pressures equivalent to 35,000 feet altitude, provided sufficient oxygen is used (15)

Resistance to breathing is approximately inversely proportional to the square root of the density. At 4 atmospheres, resistance is approximately doubled; at 0.25 atmosphere (34,000 feet) resistance is halved Healthy individuals are not aware of a change in the character of their breathing at 10 to 0.25 atmospheres unless valvular breathing apparatus is employed. Patients deriving benefit from inhalation of a mixture of 80 per cent helium and 20 per cent oxygen would experience the same degree of lessened respiratory resistance at 18,000 feet

Oxygen. Numerous tests on man have made possible a better definition of the limits of oxygen tolerance At high pressures, there is a marked increase in oxygen toxicity brought about by exercise The irritant level for prolonged inhalation of oxygen has been found to be the same for man as for lower animals, namely, about 60 per cent of 1 atmosphere (428 mm. Hg), and 100 per cent oxygen appears to be toxic (substernal distress, nose and throat irritation) after a period of about 12 hours (16) No sharp limit can be set, however, since individuals vary markedly in their response to 100 per cent oxygen The partial pressure is as important as the percentage, e g , 100 per cent oxygen not being toxic at 380 mm. Hg (18,000 feet). In one experiment, 100 per cent oxygen produced some irritation at ground level after 4 hours, but was well tolerated when continued for 24 hours at 0.25 atmosphere (34,000 feet)

At 2 5 atmospheres (50 feet diving depth) individuals at rest can tolerate oxygen for 2 hours Exercise, however, reduces the safe depth to 33 feet (2 atmospheres absolute). At pressures above 1 atmosphere the symptoms terminating oxygen exposures during either rest or exercise are nausea (40 per cent), twitchings (21 per cent), vertigo (17 per cent), visual disturbance (6 per cent), restlessness and irritability (6 per cent), numbness (6 per cent), and convulsive seizures (4 per cent) (17) The convulsive seizure, which is

with the ambient carbon dioxide (Fig. 5). During an additional 25 hours at the 5 per cent level, biochemical, physiologic, and psychologic tests show no incapacitating effects (20). The usual effects of 5 per cent carbon dioxide are a twofold to threefold increase in respiratory rate, and an increased loss of body heat due to the hyperventilation, while the subjective effects are cerebral fullness, headache, sore throat and nasal congestion, and occasionally nausea, which subside rapidly as soon as air of normal carbon dioxide content is breathed. The effects of exposure to air of a high carbon dioxide content are no greater at the end of 24 hours than they are at the end of 1 hour.

Effects of Decompression

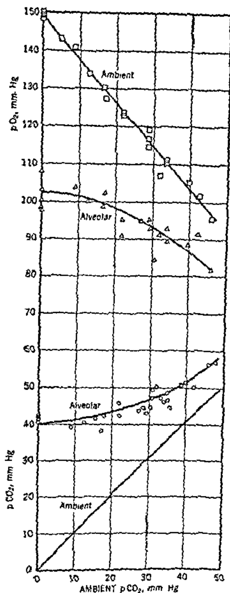
Expansion of Abdominal Gas

In early experiments on the use of helium in diving, the mouthpiece used produced salivation, so that considerable amounts of gas were swallowed at bottom depth. When these men ascended rapidly the expansion of the gas, retained in the stomach by contracted pyloric and cardiac sphincter muscles, was sufficiently great to bring about collapse (21). The impression that swallowed air or gas mixtures, rather than food (except melons, beans, and carbonated beverages), is the source of most abdominal gas has been confirmed by the subsequent studies of Blair (22) and others. The average abdominal gas content of healthy men has been reported to be about 1,300 cc., but this appears an unduly high value when one considers the fact that men in good physical condition can ascend to 38,000 feet (0.2 atmosphere) without discharging gas and without feeling distended. At this altitude, 1,300 cc. of gas *would* have expanded to about 6,500 cc. In a test in which 500 cc. of helium were introduced into the duodenum by means of a Rehfuss' tube, the degree of discomfort was similar to that occasionally experienced in an ascent from ground level to 24,000 feet, or 0.25 atmosphere (21). A more likely value for the abdominal gas content *in men with good alimentary function is 100 to 200 cc. A great deal more* work seems necessary in this field. Consideration should be given to the possible inverse relationship between abdominal gas and intestinal function, and to the fact that even minor degrees of distention, in the range usually considered normal, impairs gastric and intestinal motility.

Anoxia

The problem of anoxia, so troublesome in World War I and about which reports of progressive physical and psychologic deterioration and

rise of only about 7 mm. Hg in alveolar carbon dioxide pressure. However, 5 per cent approaches an upper limit, above which an increased rate of ventilation is no longer compensatory, so that alveolar carbon dioxide rises



mm Hg			
Ambient air		Alveolar air	
pCO_2	pO_2	pCO_2	pO_2
0 2	150 1	40 8	100 4
9 2	140 5	39 3	103 7
17 3	131 20	42 3	98 5
27 5	119 1	43 5	95 0
34 3	111 0	46 4	92 5
42 6	101 5	50 4	89 3
0 2	150 1	41 9	103 0
5 3	143 4	——	——
12 6	134 3	40 4	100 0
22 3	123.7	42 2	95 2
28 8	116 3	44 1	92 9
34 1	109 6	46 3	89 0
40 0	102 8	49 3	88 3
46 2	95 2	55 8	81 4
0 2	150 1	41 1	98 1
15 9	——	41 4	——
31 0	——	46 8	——
38 8	——	50 7	——
48 2	——	56 7	——
0 2	148 5	35 5	108 2
17 4	127 5	38 0	102 2
29 4	114 4	42 9	95 0
32 3	106 8	46 0	91 2
35 0	——	46 5	——
33 6	——	45 9	——
30 6	——	44 4	——
36 2	——	44 5	——
0 2	148 8	42 3	97 6
22 2	122 7	45 5	90 6
30 7	——	49 6	——
35 2	——	48 5	——

Fig 5. Effects of inhaled carb... ygen and carbon di-
oxide in al... of air per man was

Personnel flying aircraft not provided with oxygen equipment were admonished not to exceed 15,000 feet nor continue longer than 2 hours above 10,000 feet except in emergency (25).

Pressure Breathing. In World War II it was found necessary for some photographic missions to fly higher than 40,000 feet (equivalent to about 10,000 to 12,000 feet at air altitudes) in nonpressurized cabins. By increasing intrapulmonic pressure up to 12 inches of water above ambient pressure, useful consciousness could be maintained in the low pressure chamber at equivalent altitudes of 50,000 feet

The device commonly used for pressure breathing imposes a condition of continuous distention of the lungs in contrast with the intermittent distention, either high expiratory–low inspiratory pressure, or vice versa, familiar in clinical practice. Because it was believed that intermittent distention might be better tolerated and derange pulmonary circulation less, i e., permit better inflow of blood into the right side of the heart, various patterns of intermittent pressure were studied. It was found that a ratio of inspiratory to expiratory pressure of two to one with inspiration covering about two-thirds of the respiratory cycle was highly effective. Conversely, high expiratory–low inspiratory pressure was ineffective in maintaining oxygenation of blood At 45,000 feet, an oxygen saturation of 90 per cent could be maintained with a mask pressure of 8 inches of water at the end of inspiration and 4 8 inches of water at the end of expiration (27, 28) Alveolar carbon dioxide was about 30 mm. Hg and pulmonary ventilation was increased 50 per cent above that at ground level.

Pressure breathing, especially intermittent, also involves some degree of hyperventilation, tending therefore to increase the loss of carbon dioxide and interfering, to a certain extent, with pulmonary circulation. The loss of carbon dioxide, however, will not be serious even if respiration stops, since in an atmosphere of pure oxygen, diffusion alone will keep the blood oxygenated as effectively as during normal respiration in air. At high pressures (4 atmospheres), the toxic action of oxygen stops respiration but not the heart beat Arterial blood, for example, withdrawn from an anesthetized dog exposed to an oxygen pressure of 4 atmospheres, contained at the end of a 14 minute period of apnea 6 volumes per cent of oxygen in physical solution or only 1 volume per cent less than that present during normal breathing (29). The same phenomenon has recently been described as occurring at atmospheric pressure when 100 per cent oxygen was inhaled (30) Actually, one needs only to breathe enough to prevent the carbon dioxide from rising above normal levels, but such control of respiration has not yet been practiced

fall in ceiling altitude were frequent, has been fairly well handled during World War II. The need for oxygen economy by using "demand" breathing apparatus stimulated investigation of altitude performance with respect to anoxia.

Exposures at 10,000 feet for 6 hours daily, 5 to 6 days a week over a period of 4 to 6 weeks, have produced remarkably few real signs of deterioration, although Halstead (23) has reported extended impairment in the dynamic visual field reflected by an inability to perceive peripheral targets which previously had been readily detected. At higher altitudes, the dimming of the brightness of the visual field is one of the most constant subjective manifestations of anoxia and it is now recognized that the slightest degree of anoxia reduces ability to see at night.

An 85 per cent arterial saturation of hemoglobin is associated with some impairment in daylight flying and percentages below 80 (above 18,000 feet) are associated with appreciable handicap. Most men can tolerate an altitude of 18,000 feet for a half-hour, but even though they may be conscious they will be in a befogged state, and collapse may ensue if they stay up much longer.

Of 7,798 men exposed to a simulated altitude of 18,000 feet for about 15 minutes, 6.5 per cent developed syncopal reactions (24). The clinical results, including the evidence of electroencephalographs, indicated that in 10 thoroughly studied cases a high percentage of the "fainters" had disorders of the central nervous system tending toward epilepsy The hyperventilation and alkalosis rather than anoxia were suggested as eliciting the epileptoid trend. At some altitude indoctrination units, however, syncopal reactions at 18,000 feet were less than 1 per cent There is good reason to believe that purely psychic influences contribute to the vasomotor phenomena and are no more a reaction to anoxia than similar phenomena which follow the insertion of a hypodermic needle Apparently, some flight surgeons are able to present a truly horrendous picture of decompression hazards to the aviation cadet

Prevention of Anoxia. *Oxygen Inhalation* Aviation personnel in both services were thoroughly indoctrinated at training centers and in the field in the use of oxygen breathing equipment The designation of officers for oxygen equipment was an effective and practical method of ensuring proper care and employment of equipment.

Provision was made for the use of oxygen on (*a*) all flights above 10,000
8,000 and 10,000

of 5,000 feet.

The hyperventilation, however, is paid for by the loss of alveolar and body carbon dioxide pressure (32) If the normal alveolar carbon dioxide pressure is reduced from 40 mm. Hg to less than 20 mm. Hg at normal barometric pressure, dizziness, tingling of the extremities, and muscular spasms can occur. Conversely, if 5 per cent carbon dioxide is added to ambient air, oxygen percentages as low as 13 per cent may be tolerated for prolonged periods of time without impairment.

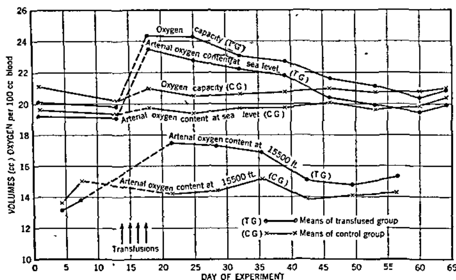


Fig 6 Mean blood oxygen capacity levels and arterial oxygen contents at sea level and at 15,500 feet of 10 men (34) Five were transfused with 2,000 cc. of a 50 per cent red cell suspension over a period of 4 days (transfused group), the remaining five transfused with an identical volume of dextrose in saline solution (control group) over the same period

Nutritional Factors No startling improvement in the altitude ceiling of man, comparable to Campbell's well-known observation of the effect of carrots on rats, can be attributed to the ingestion of any particular food, accessory food substance, or drug. A physiologic gain from a diet relatively high in carbohydrate and low in protein (10 to 15 per cent) has been accounted for by an accompanying high respiratory quotient and by the maintenance of the glycogen reserve which is so important for visual, mental, and muscular functions (33) A more important nutritional consideration than the inclusion of specific food factors is the manner in which good preparation and serving of food can influence morale.

In spite of the tendency to hyperventilate, intermittent pressure breathing appears to be more acceptable, physiologically, than continuous pressure breathing. With the latter, a vest supporting the chest has been of great help, and when combined with a closed system to prevent unnecessary loss of carbon dioxide, an intrapulmonic pressure of 33 mm Hg above ambient pressure can be maintained to provide a tolerable oxygen supply at 50,000 feet (28).

With regard to the application of pressure breathing to medical problems it has been said (26) that the increased pressure (*1*) tends to prevent exudation of fluid into the lungs and aids in returning that which has already escaped (Emerson, Barach, Carlisle), (*2*) distends alveoli which are not otherwise open, and (*3*) presumably dilates bronchioles which are abnormally constricted by muscular spasm. The first of these effects is corroborated by Rossiter's observation that a pressure of 10 mm. Hg will return the edematous fluid of burns to the blood stream.

TABLE III

EFFECT OF VENTILATION ON ALTITUDE TOLERANCE

Normal respiration (min vol 8–10 liters/min)	Arterial saturation, %	Hyperventilation* (min vol 16–20 liters/min)
10,000 ft	90	18,000 ft
15,000 ft	80	22,000 ft
18,000 ft	70	25,000 ft.

* Continuous experiment, 70 minutes at 18,000 feet, 15 minutes at 22,000 feet, and 15 minutes at 25,000 feet (31)

A study of the retarding effect of pressure breathing plus oxygen therapy at 0.5 atmosphere (18,000 feet) on the development of pulmonary edema should prove interesting Since 100 per cent oxygen is not toxic at this altitude, any respiratory resistance factors are considerably reduced, and all the important pressure differences are still maintained

Hyperventilation The most important variable affecting altitude ceiling is minute volume of respiration. Unless the degree of pulmonary ventilation is controlled, other factors which may affect the ceiling cannot be evaluated. Arterial saturation at 18,000 feet may be the same as at 13,000 feet solely as a result of hyperventilation. The failure to control minute volume of respiration has been the major factor underlying the variability of results of psychomotor test procedures used to estimate altitude tolerance. The effectiveness of hyperventilation when using a respirator to increase altitude tolerance is shown by the data in Table III

tors—pressure differential and flight altitude—regulate the extent to which gases in hollow viscera expand The damaging effect on lungs expanded beyond physiologic limits (which appears to be 2.3 times the initial volume) was found to depend upon the rate of decompression. The effects from any expansion less than 2 3 times the initial volume were independent of decompression rate.

At the moment of decompression, subjects experience a sense of inflation in their chest and abdomen and a rush of air from mouth and nose. Abdominal gas pain is surprisingly uncommon.

TABLE IV

CONDENSED DATA OF EXPLOSIVE DECOMPRESSION EXPERIMENTS ON HUMAN BEINGS (35)

Diam of opening in 45 cu ft cabin, in.	Differential pressure, lbs /sq in	Simulated altitude, ft		Time of decompression, sec	Expansion of body gases by
		Cabin	Flight		
12	6 55	10,200	35,000	0 075	3 5
12	7 50	8,000	35,000	0 090	3 9
27	1 50	34,000	45,000	0 008	2 3
27	1 25	37,000	48,000	0 006	2 3
27	1 00	40,000	50,000	0 005	2 3

Pneumothorax. Spontaneous pneumothorax may occur in the distended lung during rapid decompression In studies in rats of the mechanism of pneumothorax following rapid decompression from high pressure oxygen atmospheres, a high incidence of atelectatic lungs (7 out of 400) was observed (36) The primary injury appeared to be a rupture of a few alveoli with the passage of gas beneath visceral pleura to the mediastinum, followed by rupture of mediastinal pleura to permit entrance of gas into the thoracic space How differential pressure sufficient to rupture alveoli is attained is rather puzzling, in view of man's remarkable tolerance to explosive altitude decompression

The 2 3 ratio found by Sweeney agrees roughly with the figure during ascent from depths If Sweeney's subjects were breathing normally, the maximal normal volume would be twice the contained volume. It has been calculated that when the breath is held in ascent from depths, the lungs can be distended to roughly one-third greater than the maximal normal volume without rupture. Hence, in submarine escape training, death has occurred in rapid ascent (presumably with breath holding) from depths as shallow as 15 feet On the other hand, if exhalation is continuous, ascents can be

Injection of Red Blood Cells. Transfusing suspensions of red blood cells into normal men appears to be a most effective method of diminishing the degree of anoxia and bringing about an apparent state of artificial acclimatization to altitude (34). By this procedure it was possible to increase significantly both the oxygen capacity and oxygen content of the blood (Fig. 6). The oxygen saturation of the arterial blood, both at ground level and at altitude, was not reduced by the resultant plethora. In other words, the hemoglobin of the entire mass of red cells including those added

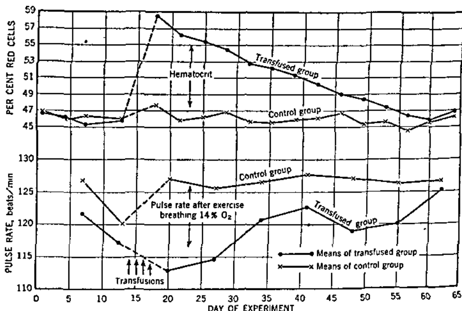


Fig 7 Mean blood hematocrit levels and pulse rates of 10 men after exercise when breathing 14 per cent oxygen (34) A group of 5 men were transfused with 2,000 cc of a 50 per cent red cell suspension over a period of 4 days, the other 5 transfused with an identical volume of dextrose in saline solution (control group) over the same period

by transfusion was being effectively oxygenated During the polycythemic period, the pulse rate following exercise when breathing low oxygen mixtures was significantly lower than control measurements (Fig. 7). The polycythemia persisted approximately 6 weeks

Explosive Decompression

In pressurized aircraft, the possibility of sudden loss of pressure differential creates the hazard for the aviator of explosive decompression An analysis based upon extensive experiments (Table IV) showed that two fac-

while to review experiments on gaseous exchange in man and the pathologic changes in lower animals.

Physiologic Aspects of Decompression Sickness. Studies of inert gas uptake and elimination are essential for the development of measures to prevent decompression sickness Such studies also provide the basic data for the understanding of the uptake of anesthetic gases, and for estimations of body fat content; they hold promise, as well, of reflecting changes in circulatory rate and of making possible estimates of cardiac minute volume. The recent employment of radioactive gases, with its simplicity and precision of technic, should facilitate investigations of cardiorespiratory function, which ultimately may be clinically applicable.

Solubility Coefficients and Inert Gas Content of Body. Inert gases are soluble in body fluids and fat. The ratio of gas solubility in fat to that in water (blood) is a most important factor governing both its absorption and its elimination from body tissues. Potent anesthetic gases, e.g., cyclopropane and chloroform, which, like gaseous nitrogen, behave as chemically inert substances, have ratios of the order of 35 to 1 The ratio for ether is 4.3 to 1, so that a sevenfold increase in desaturation time following anesthesia should be required for cyclopropane in comparison with ether. Thus, fat constitutes a huge potential gas reservoir, the size of which can be estimated approximately from measurements of gaseous nitrogen dissolved in body tissues and from the specific gravity of the body as a whole. For example, for a diver weighing 70 kilograms, with a specific gravity value of 1.060, the body fat, computed on the basis of the formula:

$$5(1.100 - 1.060) \times 70$$

is found to be 20 per cent of the total body weight, or 14 kilograms The body fluids, computed by the formula:

$$0.724(70 - 14)$$

amount to 40.54 kilograms. To compute the body nitrogen content we need only multiply the values for the body fat and water contents by their respective solubility coefficients:

$$14 \times 55.7 = 779.8 = \text{"fat" nitrogen}$$
$$40.54 \times 9.0 = 364.9 = \text{"fluid" nitrogen}$$
$$1144.7 = \text{estimated total nitrogen (cc)}$$

This estimate could be checked by measuring the quantity of nitrogen exhaled by the diver into a Douglas bag or spirometer while breathing 100

made from depths of 100 feet (4 atmospheres) to the surface in 20 seconds or less without mishap. Breath holding during underwater ascent creates a sensation of substernal distress and a feeling that the lungs are actually stretched. In experiments on dogs, overdistention of the lungs with intrapulmonic pressures of 80 mm. Hg applied for 10 seconds was followed by the presence of gas bubbles in the carotid arteries (37).

Safe Pressures. Using the criterion of substernal distress as an index of pulmonary overdistention, it has been found that intrapulmonic pressures of 10 to 15 mm. Hg applied for 5 seconds are well tolerated by healthy men [illegible] During pressure [illegible] of 8 inches of [illegible] erdistention of lungs appears to be an essential factor in the development of air embolism, since the "splinting" of the abdomen and thorax renders high intrapulmonic pressures safe.

Decompression Sickness

Rapid decompression of divers and compressed-air workers may give rise to the formation of bubbles in the blood stream and fatty tissues. Considerable experimental data indicate that intravascular bubbles elicit characteristic symptoms of pain (bends), asphyxia (chokes), and paralysis. When aviation personnel are decompressed rapidly from the ground level to high altitudes, they also develop, with the exception of paralysis, identical but usually less severe symptoms. Minor signs are pruritus and skin rash, prone to occur if the skin is chilled during decompression.

Since the classic experiments of Paul Bert, it has been generally accepted that the absorbed gas can form bubbles in the blood and tissues during *rapid decompression*. The real problem now is whether the gas bubbles responsible for the symptoms of compressed air illness are chiefly intravascular or extravascular.

Intravascular bubbles have been observed at autopsy in divers and caisson workers. In altitude decompression, however, bubbles have not been observed in man, although sludge formation (pseudohemagglutination within the vessels) has been observed and x-rays have shown the presence of gas in joint spaces and in tissues (38). Some experienced clinicians attribute the symptomatology of decompression sickness entirely to extravascular bubbles (39).

Because of the protean nature of the symptoms and the fact that the only specific therapeutic measure, recompression, promotes such dramatic recovery in the asphyxiated, pulseless, cyanotic patient, it seems worth-

lies in the reproducibility of results and the frequency and accuracy of individual readings

Inhalation of Radioactive Gas following Occlusion Test. If the blood supply to the hand and arm is occluded for 10 minutes, the inhalation of radiokrypton either at the start of or following occlusion reveals the effect of reactive hyperemia on gas absorption, as shown by Figure 9 (32). The most influential factor in the difference in rates, as shown in curves *A* and *B*, appears to be the effectiveness of peripheral blood flow. Following the return of the blood supply to the arm, it may be assumed that capillary beds, normally quiescent, open up so that the transported gas is able to

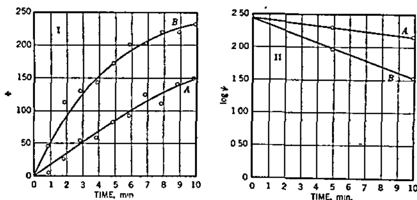


Fig 9 Absorption of inhaled radiokrypton by tissues of hand (40). I: *A* is normal curve of uptake of radiokrypton by resting individual during 10 minute period, ordinate represents counts of a Geiger counter held in the hand *B* is the uptake of the gas in same resting individual following resumption of blood flow which had been cut off by means of a tourniquet on arm for 10 minutes II· Semilogarithmic plot of same data The slopes of *A* and *B* indicate relative rates of gas uptake

diffuse into large areas of unsaturated tissue The difference in saturation rates according to curves *A* and *B*, or between the quiescent and active capillary beds, may prove to be least in men possessing the highest peripheral blood flow under basal conditions The application of these studies of gaseous absorption and elimination should give additional information on cardiac output, blood flow to the skin, and the distribution and quantitative uptake of anesthetic gases

In Vivo Observations In dogs rapidly decompressed from high atmospheric pressure (60 pounds gage), at first small bubbles can be observed circulating rapidly through cutaneous arteries and veins; later, bubbles of gradually increasing size are found to slow down and eventually stop cir-

per cent oxygen. Over a period of 12 hours, 1,076 cc. of nitrogen were collected in this manner.

When oxygen is inhaled and successive samples of exhaled air over given periods of time are collected in spirometers and analyzed for their nitrogen content, a curve of the rate of nitrogen elimination can be obtained. Curve *A* proves to be exponential (Fig. 8); it can be conveniently divided into two components, *B* and *C*, which approximate the manner in which gaseous nitrogen is absorbed or eliminated from its chief body solvents—water and fat (40).

Cutaneous Diffusion of Gas. Nitrogen diffuses through skin at the rate of 10 to 15 cc. per hour. This fact, ascertained during the inhalation of

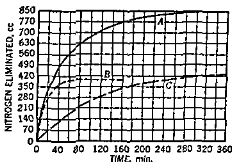


Fig. 8. Elimination of nitrogen from the body during a course of oxygen inhalation (40). Curve *A* is drawn through the experimental values, curves *B* and *C* are hypothetical. The values of *A* are the totals of the corresponding values on *B* and *C*, representing "fluid" and "fat" nitrogen, respectively.

oxygen by mask, when the body was surrounded by air and small amounts of nitrogen continued to be eliminated indefinitely, suggested a method of estimating cutaneous blood flow by using a more rapidly diffusing gas, such as helium. This gas proved to be nearly ideal, since it diffuses rapidly into the subcutaneous capillaries on contact with the skin and can be collected from the lungs in sufficient quantities to allow computation of cutaneous blood flow by dividing the amount of helium so collected by its solubility coefficient in blood.

Absorption of Radioactive Gas. If a tracer gas, such as radiokrypton, is inhaled, its absorption can be followed precisely in a given region of the body, e.g., the hand, by a technic first used by Lawrence and Jones of the Aeromedical Laboratory of the University of California. The absorption curve obtained during a period of at least 30 minutes on the basis of Geiger counts is similar to that of nitrogen and helium. The value of the technic

In rabbits decompressed to a simulated altitude of 45,000 feet in 3 to 30 seconds and in 2 to 7 minutes there was, in contrast with the high pressure experiments on guinea pigs, no constant relationship between fat content and the quantity of gas bubbles. Only intravascular bubbles were found under these test conditions (46)

Variables Affecting Bubble Formation. In man, the underlying factors responsible for bubble formation fall into two groups In the first are those conditions which increase gas content of tissues, namely, the amount of fat and the degree and duration of exposure to pressure. In the second are variables relating to blood circulation (effective blood flow), the transport of gas from tissues, and the tendency of bubbles to form (tissue trauma, muscular strain). Thus age, time of day, temperature, fright, injury of tissue, and the postalcoholic state have real influence on the incidence of bends. The most important factor in altitude decompression is exercise; this serves to increase the carbon dioxide content of tissues and to raise the *20 to 25 per cent incidence of bends to 60 to 70 per cent*

Routine training test exposures of 1.5 to 3 hours at a simulated altitude of 38,000 feet show that (*a*) 18 year old individuals are less susceptible to bends than those 26 years of age (18 per cent as compared with 30 per cent), (*b*) the incidence of bends may be twice as high in the morning as in the afternoon, (*c*) fright (peripheral vasoconstriction) predisposes to occurrence of bends, and (*d*) bends are more apt to occur at the site of tissue injury. These facts support the concept that what may be termed "effective blood flow" through tissues is the common denominator explaining not only variation in susceptibility in different individuals but in the same individual repeatedly subjected to the stress of decompression. The effect, for example, of reactive hyperemia on the rate of gas absorption illustrates the range of variation in capillary blood flow even in resting tissues

The differences in tolerance of various animal species to rapid decompression following saturation exposures to high pressure atmospheres may be ascribed to variations in effective blood flow through tissues. Man tolerates a sudden drop from pressure of 2 atmospheres to 1; for the dog and cat, the ratio is 4 to 1; for the guinea pig, 5 to 1; and for the mouse, about 6 to 1. The pattern of tolerance roughly follows the relationship of basal metabolism to unit of body weight

Classification Tests for Susceptibility to Decompression Sickness In view of the many factors affecting peripheral circulation, pressure chamber tests to determine resistance to bends have generally failed to predict the reaction of any given individual in any single exposure Highly susceptible or resistant individuals can be selected by present methods, but the inter-

culating Bubbles have also been observed in the cerebral vessels of monkeys fitted with leucite calvaria (41), and through a Forbes window in the pial blood vessels of cats (42). Sludge formation, or the close grouping of red blood cells in compact masses separated by zones of clear plasma, accompanies the reduction in blood flow (42). This phenomenon apparently occurs under a variety of conditions associated with slowed circulation, plasma loss, and cell packing

Histologic Observations. In studies on guinea pigs rapidly decompressed from high pressure atmospheres, intravascular gas bubbles occurred in all tissues and organs but were far more numerous in those rich in fat. Extravascular bubbles were observed only in tissue rich in fat, in the lipid matter of the adrenal cortex, and in the myelin sheaths of nerve fibers (43).

Gas bubbles may be present in the blood vessels only and not extravascularly in fat; fat guinea pigs, in comparison with lean animals, not only show extensive intra- and extravascular bubble formation but bubbles form in the fat guinea pigs at considerably lower decompression levels These histologic studies definitely demonstrate the capacity of fat to act as a gaseous reservoir. Moreover, the total capillary bed of tissue rich in fat is only one-third as great as the capillary bed of muscle. The capillary bed of tissue poor in fat has about the same density as that of the most poorly supplied muscle, hence potential gas transport from fatty tissue is poor (44).

Apart from bubbles and sludge formation, the only other morphologic change in tissue as a result of rapid decompression is the finding of large water vacuoles in the cytoplasm of liver cells, but the significance of this finding is as yet unknown

The x-ray appearance of tissues in rapidly decompressed individuals may have been misinterpreted in view of studies on guinea pigs in which it was concluded that (*1*) bubbles in blood vessels are recognizable in x-rays, and (*2*) *bubbles in fat or other forms of connective tissue are usually recognizable* only as a general x-ray shadow (45) Tissue or extravascular bubbles are rarely recognizable as such; in human tissues the small bubbles *in fascial planes, for example*, may appear to be extravascular and yet be located in small blood vessels.

Quantitative Evaluation of Bubble Formation Decompression of guinea pigs in 4 seconds from pressure levels of from 60 to 105 pounds per square inch was associated with a decrease in specific gravity in proportion to the amount of fat present (43) When bubbles were present, the specific gravity of fat tissue was reduced from 0 95 to 0 65, of adrenal gland from 1 045 to 0.97, and of the whole guinea pig from 1 050 to 1 000

ference with nutrition occurring secondarily to the interruption of blood supply by liberated nitrogen.

In divers suffering repeatedly from experimental bends, no characteristic lesions were found in a roentgenologic study at different periods following the tests Some factor, such as multiple repeated injury, concomitant infection, or anomalous blood supply may operate in conjunction with embolism to produce the described changes The analogy that may be drawn to the relationship between the ingestion of alcohol and cirrhosis of the liver suggests the type of analysis required to evaluate the finding.

The fact that gas emboli interfere with the blood supply to muscles and other tissue is also consistent with the symptoms of bends, especially those which occur in rapid decompression in a helium atmosphere. The decreased solubility of helium in fat decreases the incidence of bone lesions. It is also true that, following helium dives, the upper extremities are more frequently afflicted with bends than they are following compressed air dives Swelling of the arms is not uncommon and crepitus has been felt over the brachial veins, suggesting partial blocking of venous return Vasoconstriction of cutaneous vessels is evident by the pallor and fall in skin temperature

Fatigue, which may be prodromal or subsequent to bends, is a symptom of especial interest In experimental borderline decompressions, fatigue is frequently the first sign of excessive bubble formation In association with bends, fatigue may take the form of an exhausting malaise combined with chills, fever, and sweating Following diving decompression, it is regarded as subclinical bends, it can be prevented by slow decompression. Fatigue was regularly recorded by altitude physiologists who, early in training programs, cut down the frequency of their exposures from daily to weekly runs or even only occasional appearances in the low pressure chamber This type of debilitating fatigue—referred to by Armstrong (51) as the "x" factor—frequently noted in exposures above 20,000 feet, can be prevented by a long enough inhalation of oxygen prior to ascent to "wash out" most of the dissolved nitrogen in the body

Paralysis The chief difference between altitude and diving decompression symptoms, apart from severity, is that the paralysis which not infrequently affects the lower part of the spinal cord in divers and caisson workers has not been reported in the hundreds of thousands of altitude training tests

A diver, following decompression, may remain in apparently good condition for several hours and then collapse because of paralysis of the lower extremities Immediate and prolonged recompression usually brings about

mediate group cannot be classified accurately until the various factors affecting individual performance are controlled. Again one may subscribe to the general conclusion regarding all tests applied to healthy men, namely, that while group comparisons and the average of a series of performances may have high retest reliability, individual variation precludes precise prediction of individual performance in any given test

Symptomatology. *Bends.* The most common manifestation is a dull, throbbing type of pain, gradual in onset, progressive and shifting in character, and frequently felt in the joints or deeply in muscles and bones. Pain or pains of this nature are referred to as "bends," a term established by usage to denote a well-recognized clinical entity and used interchangeably with decompression sickness Prior to the onset of pain, there may be, particularly in the joints, paresthesia frequently described as numbness or merely an awareness that "something is not right." The skin temperature falls either prior to or during the period of pain and the involved part becomes blanched in appearance If the upper extremities are involved, there is likely to be a fall in temperature and decreased blood flow in the fingers

The following experience illustrates the similarity between diving and altitude bends A diver breathing a helium–oxygen mixture for 30 minutes at a depth of 400 feet was decompressed too rapidly. His chief complaints were pain, swelling, and limitation of motion confined to the right ankle *Several days later he served as a subject for rapid decompression to a simu*lated altitude of 38,500 feet. This test was terminated after 46 minutes because of intense pain in the right ankle

Bone is the most likely location for bends to occur, particularly the marrow with its high absorption coefficient for nitrogen and its sluggish, sinusoid type of circulation From the point of view of body economy, bone is the tissue that renders man unsuited for long exposures in compressed air.

An intensified pain in bones experienced by some subjects during early recompression treatment is believed to arise from a "squeeze" of bone marrow due to such rapid compression of bubbles that body fluids cannot immediately replace the suddenly diminished gas volume within *the bone* cortex

The characteristic bone lesions (47–50) in caisson workers support the view that the symptoms giving rise to bends originate, in part at least, from *ischemic changes in bone* Lesions in the diaphyses and epiphyses of long bones, which are painless unless complicated by joint involvement, have been described, and are attributed to aseptic necrosis of bone or inter-

sometimes observed at 18,000 feet when air is breathed, since recovery is delayed.

Recompression and judicious administration of fluids have brought about *recovery of divers seemingly in extremis* To treat the *shock syndrome* in aviation personnel, more pressure than that involved in descent to ground level is often required.

According to Heller, Mager, and von Schrotter (53), the effect of gas in the pulmonary vessels is to displace blood and inflate the lungs intravascu-

TABLE V

RELATIONSHIP BETWEEN NITROGEN BUBBLE FORMATION, RESPIRATORY RATE, AND BLOOD PRESSURE IN DOGS RAPIDLY DECOMPRESSED FROM HIGH ALTITUDE ATMOSPHERIC PRESSURES

Experiment No	Time after decompression, minutes	Respiratory rate	Blood pressure	Compression, prior to decompression	
				Lbs /sq in	Hours
2	12 36	20 20	110 110	45	4*
4A	4 8 14 17 21 25 94 200	24 22 34 24 50 54 36 19	Values remained between 120-130 mm Hg	60	1 5
4B	3 7 25 33 37 45 46	14 14 9 8 7 7 Failure	124 120 140 60 40	60	2
6A	3 11 14 27 19 21 26 32 36 58	7 19 20 38 69 78 92 47 17 11	90 112 90 90	60	2
6B	1 3 Recompression	9 Failure	64 110-25 120 92 88	75	0 55

* Dog in good condition the following day

recovery, even following paraplegia of the lower extremities Dogs rapidly decompressed from high pressures and then only partially recompressed (just sufficiently to prevent death from asphyxia) frequently develop paralysis of the hind legs, foot drop, a spastic type of gait, and paralysis of the bladder musculature. In both dog and man incompletely recompressed following massive embolism, residual symptoms may persist for months.

Although vertigo, deafness, occasional aphasia, and transient visual disturbances have been recorded, permanent impairment as a result of brain injury, in contrast with spinal cord lesions, are rare Within the spinal cord itself the regions of relatively poor blood supply, i e , the lower thoracic and upper lumbar, are the ones most frequently involved.

Clinical conditions manifesting symptoms similar to those associated with the presence of air emboli in the spinal cord are tabes dorsalis and arteriosclerosis of the terminal aorta involving the lumbar segmental arteries Reichert *et al* (52) have described the conditions of four patients who, on exertion, exhibited weakness of the thighs not accompanied by pain, associated with normal pulsation of the femoral arteries These patients, however, showed extensive calcification of the terminal aorta That the weakness was due to interference with the blood supply was confirmed by an experiment in which a similar syndrome was produced in dogs following ligation of the lumbar segmental arteries

Chokes and the Shock Syndrome The most interesting manifestation of decompression sickness is a type of asphyxia designated most aptly by the early caisson workers as "chokes" This symptom occurs less frequently than bends because it does not develop until rather large quantities of gas have moved from the peripheral circulation into the large veins, the right side of the heart, and the pulmonary vessels Thus, several hours of complete well-being may elapse after decompression before the appearance of the earliest symptoms of chokes This symptom, which has proved most useful, is a sensation of substernal distress felt only during deep inspiration, frequently eliciting the cough reflex The sensation may be only transient or it may progress to frank asphyxia Normal breathing becomes shallow, rapid, and then dyspneic Paroxysmal attacks of coughing, or true chokes, may precede loss of consciousness

Untreated chokes, with or without bends, in compressed air workers is not infrequently attended by the cold moist skin, signs of impaired circulation, and hemoconcentration associated with surgical shock Similar signs preceding collapse are occasionally observed in aviation personnel in pressure chambers either at altitudes above 35,000 feet or subsequently on return to ground level The collapse is not the anoxic response which is

to propel blood through an obstructed pulmonary bed. The absorption of bubbles by compression and by oxygen inhalation leaves the animal in good condition unless irreparable damage has been done to the heart by oxygen lack or by increased pulmonary resistance, or to the spinal cord by ischemia.

Treatment of Decompression Sickness. The objectives in treatment are immediate and prolonged recompression and the judicious employment of oxygen and fluids The outline in Table VII is the culmination of several years' work at the Experimental Diving Unit, Navy Yard, Washington, D C, and the Naval Medical Research Institute (54) It has been used repeatedly and effectively for the treatment of severely distressed and occasionally moribund divers and compressed air workers.

The most frequent errors in treatment are (*a*) failure to treat doubtful cases, (*b*) delayed recompression, (*c*) failure to treat the serious cases adequately according to columns 3 or 4 of Table VII, and (*d*) failure to keep the treated diver near the chamber for a 24 hour period

Prevention of Altitude Decompression Sickness. In a group of 20 men (average age 30 years) exposed in an altitude chamber to 38,000 feet, the occurrence of bends regularly forced the descent of all members of the group to ground level within a period of 3 hours (55). However, when oxygen was inhaled for 4 hours prior to ascent, decompression sickness and fatigue were prevented for as long as 12 hours in all but one, this man was suffering from an old leg injury and required 6 hours of oxygen inhalation for protection In younger age groups (aviation cadets) inhalation of oxygen for 1 hour periods afforded nearly complete protection for 2 hour exposures at 38,000 feet

Thus, it would seem that the removal or "washing out" by oxygen inhalation of the nitrogen dissolved in the body tissues, in order to render susceptible individuals resistant to the incapacitation which otherwise occurs, constitutes the essential link in the proof that gaseous bubbles (presumably intravascular) underly the etiology of decompression symptoms at high altitude The procedure also obviously affords an excellent preventive measure

Acceleration

When a plane at high speed alters its path, a centrifugal force is exerted on the pilot's body as a result of inertia This is known as the force of acceleration and is conveniently expressed in multiples of normal gravitational force, *g* It is determined by the formula

$$F \text{ (accel.)} = V^2/32.2r$$

larly, thus producing a decreased alveolar ventilation The shallow breathing may therefore tentatively be regarded as primarily the result of reflex stimuli initiated by alternate distention and contraction during inspiration and expiration, respectively, of vessels containing gas. This hypothesis is supported by the disappearance of symptoms with recompression (sometimes with oxygen inhalation), and the presence of pulmonary bubbles in association with rapid, shallow breathing in dogs. In fact, a series of experiments using rapidly decompressed dogs has contributed considerable information about this symptom of chokes. During the period of tachypnea following rapid decompression, the pulse rate falls and the blood pressure shows an asphyxial rise and then a fall (Tables V and VI).

TABLE VI

PHYSIOLOGIC EFFECTS OF DECOMPRESSION IN 5 TO 6 SECONDS OF A DOG *EXPOSED FOR 105 MINUTES TO A PRESSURE OF 65 LBS PER SQ IN*

Period	Respiratory rate	Blood pressure	Arterial pCO_2	Hemoglobin O_2 saturation, %	Arterial-venous O_2 difference	O_2 capacity
Control	20	116	45	*90	3 6	22 8
Postcompression	142	140 to 30	59	24	6 9	26 1
Recompression	40	90	56	88	11 7	27 3
Following recompression	125	100 (O_2 therapy)	59	26	19 6	29 8

In these experiments blood samples were drawn from the femoral artery and from the right atrium or ventricle by means of a glass canula inserted into the external jugular vein Of particular interest was the occurrence of hemoconcentration, as shown by the increased oxygen capacity of the blood (Table VI) In some tests it amounted to as much as a 30 per cent increase in cell volume The hemoconcentration was thought to be due to a loss of fluid through capillaries damaged by asphyxia and possibly to an increased mobilization of red blood cells from the spleen The blood, moreover, was difficult to withdraw because of the tendency to clot In histologic sections of the lungs, cell packing in blood vessels was a consistent finding. The increased arterial–venous oxygen difference (Table VI) is an indication of the slow circulation rate The low values for arterial oxyhemo- [illegible]

Essentially, the maintenance of [illegible]
ments depends upon the integrity of the right ventricle, and upon its ability

in which V is velocity in feet per second and r is the radius of the turn in feet (56). The successful protection of aviators against the onset of distress from changes in velocity is apparently *the* factor in our aviation medical research development that chiefly contributed to our superiority over the enemy in tactical operations. The pioneer studies of Captain John R Poppen (MC), USN, in the laboratory of the Harvard School of Public Health and in aircraft, in 1933, provided basic physiologic data, of which measurements of changes in blood pressure during flight were the most ingenious The basic principle was established that by applying pressure to the abdominal area with a belt blood pooling could be circumvented. This procedure seemed to be the most direct way of overcoming the blackout resulting from gravity stress However, in the early trials the abdominal belt failed to prevent blackout. Professor Krogh, who at the time was visiting the laboratory, believed that pressure had not been applied early enough to move venous blood from the splanchnic area through the restraining capillary bed of the liver and suggested that it be applied before acceleration began Pressure applied some 30 seconds before acceleration proved effective, and additional protection has been afforded since then by including the lower extremities in the pressurized system It still required a great deal of effort and time (1941 to 1944) to provide a garment acceptable to aviators and effective in aircraft The close cooperation between Army and Navy officers, civilian scientists, and a manufacturer is an outstanding example of coordinating flight tests, laboratory studies, and commercial development to make use of scientific principles in the design and production of practical and acceptable products The physiologic studies conducted in the course of developing the anti-g suit have provided some of the most intriguing data of the war in regard to the effect of a military stress on man.

Illustrative of the type of machine that has been most useful in studying the effects of centrifugal force is the human centrifuge at Wright Field which can impart to a load of 400 pounds a force 20 times that of gravity. The linear speed attained in the cab station is approximately 90 miles per hour, and this speed can be obtained from standstill in approximately 10 seconds (57)

The tolerance for positive g (the tendency of the pilot to be pushed down into his seat) is related to both the magnitude and duration of the force applied, and may be summarized by stating that at 3 to 4 g, upward movement of the extremities becomes difficult, at 3 5 to 5 g, acting for 3 to 5 seconds, blurring and narrowing of the fields of vision precede the blackout, or loss of vision, without loss of consciousness With 3 to 5 g the

TABLE VII. TREATMENT OF COMPRESSED AIR SICKNESS

Stops		Bends (pain only)				Serious symptoms	
Rate of *descent* 25 ft per min	Rate of *ascent*, 1 min between stops	Pain relieved at depths *less than* 66 ft (29 4 lbs) Use column 1-A only when O_2 is not available		Pain relieved at depths *greater than* 66 ft (29 4 lbs) Use column 2-A only when O_2 is not available. If pain does not improve within 30 min at 165 ft (73 4 lbs) the case is probably *not* bends. Decompress on column 2 or 2-A		[illegible] he following [illegible] ieness [illegible] s [illegible] or inability to use arms or legs [illegible] disturbances [illegible] ech or hearing [illegible] rtness of breath or chokes	
						[illegible] re- [illegible] hin [illegible] 165 [illegible] s)	Symptoms *not* relieved within 30 min at 165 ft (73 4 lbs)
Pressure	Ft	Column 1	Column 1-A	Column 2	Column 2-A	[illegible]	Column 4
73 4 lbs	165			30 (air)	30 (air)	[illegible]	30 to 120 (air)
62 3	140			12 (air)	12 (air)	[illegible]	30 (air)
53 4	120			12 (air)	12 (air)	[illegible]	30 (air)
44 5	100	30 (air)	30 (air)	12 (air)	12 (air)	[illegible]	30 (air)
35 6	80	12 (air)	12 (air)	12 (air)	12 (air)	[illegible]	30 (air)
26 7	60	30 (O_2)*	30 (air)	30 (O_2)*	30 (air)	[illegible] (air)	6 hr (air)
22 3	50	30 (O_2)*	30 (air)	30 (O_2)*	30 (air)	[illegible] (air)	6 hr. (air)
17 8	40	30 (O_2)	30 (air)	30 (O_2)	30 (air)	[illegible] (air)	6 hr. (air)
13 4	30	↓	60 (air)	60 (O_2)	120 (air)	[illegible]	First 11 hr. (air), then 60 (O_2) or (air)
8 9	20	5 (O_2)	60 (air)	↓	120 (air)	120 (air)	First 60 (air), then 60 (O_2) or (air)
4 5	10	↓	120 (air)	5 (O_2) ↓	4 hr (air)	120 (air)	First 60 (air), then 60 (O_2) or (air)
Surface							

Time at all stops in minutes unless otherwise indicated

If symptoms return while breathing air *during* treatment with any of the above tables, recompress to depth of relief but never less than a depth of 30 ft and then complete decompression from this depth according to column 4.

* If dizziness, nausea, muscular twitching, or blurring of vision occurs while breathing oxygen, remove mask and proceed as follows (a) if using column 1, complete remaining stops of column 1-A, (b) if using column 2, complete remaining stops of column 2-A (c) if using column 3, complete remaining stops of column 3 breathing air At the discretion of the medical officer, oxygen breathing may be resumed at the 40 and 30 foot stops for a total of 90 minutes if using column 1 or 3 and 150 minutes if using column 2

Should symptoms recur *following* treatment with any of the above tables, recompress the diver to a depth giving relief If relief occurs at depth less than 30 feet, take diver to 30 feet and decompress from 30 foot stop to surface according to column 3 If relief occurs at *deeper than* 30 feet, remain at the depth of relief for 30 minutes and then complete remaining stops of column 3 using air throughout

able bladders affords the greatest amount of protection (61). The degree of protection afforded can be increased by $2g$ if pressure is also applied to the lower extremities. Application of pressure to the lower extremities only affords barely perceptible protection Based on these findings, simple, inflatable bladder assemblies, properly operated with respect to accelerative force, have been constructed It is this sort of equipment which has given our pilots superiority during turning maneuvers in combat.

Cold

Cold has been one of the formidable causes of temporary and often permanent incapacitation in aviation. With air temperatures of −35 to −45 C. and rapid air flow at altitudes between 25,000 and 30,000 feet, the protection of the hands, especially, has taxed the ingenuity of physiologists

After many unsuccessful attempts to make wool and leather garments sufficiently warm to afford protection, it became evident that the bulk required was so great as to make them useless. Electrically heated suits were apparently essential It was also found necessary to heat not only the body, but the hands and feet as well, according to carefully worked out patterns of heat distribution

The hands and feet appear to be body thermostats At subfreezing temperatures, tolerance time depends to a large extent upon the rapid cooling of the hands and feet A skin temperature of about 50 F. is the lower limit of temperature at which a reasonable degree of manual dexterity can be maintained About 60 F is the limiting air temperature for prolonged exposure of feet to cold when the body is lightly clothed.

Physiologic studies have shown that the volume of blood flow is least when the hands are moderately cold (15 to 20 C.); when the hands are very cold (10 C or below) the volume of blood flow is approximately equal to that of warm hands Changes in body temperature (trunk) do not disturb this relationship, but at lower body temperatures blood flow to the hand is considerably less than it is at high body temperatures (62) Frostbite or freezing of tissues has not been encountered until the ambient temperature is in the range of −10 to −20 C

Treatment of frostbite is in accord with principles suggested by the physiologic data, namely, the application of gentle warmth (10 to 15 C), but not heat, in order to prevent a rapid flow into greatly dilated and highly permeable capillary beds and in this way diminish the tendency to edema formation

In arctic operations, flyers falling into cold water (5 to 10 C) have died in less than 30 minutes. If the temperature of the water is 20 C,

physiologic effects are produced in the first 10 seconds; after that, compensatory cardiovascular forces come into action and operate to clear up visual symptoms even though the positive accelerative force continues With 7 to 9 *g*, man's limit without protective devices is reached and blackout may occur within 2 seconds (58). A clear differentiation can usually be made between blackout or loss of vision with hearing and orientation maintained, and loss of consciousness. In the former there is immediate recovery from blackout following removal of the *g* force, but following loss of consciousness it is delayed. A remarkable parallel exists between the visual symptoms in oxygen poisoning attendant upon prolonged exposure at 3 atmospheres pressure (subconvulsive level) and the blackout produced by centrifugal force. The loss of consciousness in oxygen poisoning, however, is accompanied by violent convulsive seizures, in contrast with the minor muscular movements of a clonic character due to the *g* force.

The effect of acceleration on the central nervous system results from temporary cerebral ischemia and not from temporary brain injury due to pressure Lambert (59), by an ingenious method of applying air pressure to the eye, measured the effective systolic pressure to the eye (systolic pressure at the head level minus applied eye pressure) and found the following relationship with reference to symptoms:

Effective systolic pressure, mm Hg	Symptoms
49 to 30	Vision dim
32 to 20	Peripheral vision lost
20 to 0	Vision completely lost

On the centrifuge, the application of 20 to 30 mm Hg pressure to the eyeballs lowered the threshold acceleration at which visual changes of *g* occur by 1 *g* This amount of pressure corresponds to the fall in systolic pressure per unit of *g* at the head level during exposure to acceleration. The application of 30 to 40 mm Hg suction prevented the occurrence of blackout. It would appear, therefore, that loss of vision (blackout) is the result of retinal, rather than of cerebral, ischemia.

Protection against the *g* force resolves itself into measures which maintain retinal and cerebral blood flow Voluntary measures that produce a temporary hypertension and aid venous return, such as forcible contraction of abdominal muscles, may enable individuals to maintain vision at 9 *g* During centrifuge runs, protection can also be provided by immersion in water in the sitting position The degree of protection afforded is about 0.9 *g* and 1 7 *g* when the water levels are at the xyphoid and third rib levels, respectively (60). Pressure to the abdomen and trunk applied by inflat-

of deciding upon the limiting concentrations of carbon monoxide consistent with good military performance

The work of Haldane, Henderson, Drinker, and others have demonstrated not only the relationship between symptoms of carbon monoxide poisoning and the blood concentration of carbon monoxide, but also the quantitative nature of carbon monoxide uptake which makes possible a method for determination of blood volume There remained, however, the problem of investigating the absorption of relatively high concentrations over short periods of time The chief contributions to aviation practices arising from these investigations were an accurate definition of, and a statement governing, the relationship between the variables involved in the

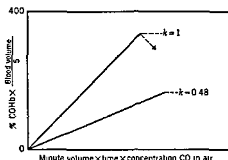


Fig 10. Amount of carbon monoxide taken up by the blood plotted against the quantity of carbon monoxide inhaled (40) The slope of the line is governed by the fraction of carbon monoxide taken out of the inhaled air This relationship holds for a carboxyhemoglobin saturation of at least 30 per cent (about 400 cc CO). $k = 0\ 48$ was the average value for a group of healthy men studied

carbon monoxide absorption for blood levels up to at least 30 per cent (65, 66) Thus, the physiologic stress created by the inhalation of carbon monoxide can be accurately estimated For any given exposure time in minutes, t, the quantity of carbon monoxide inhaled will be.

$$\text{respiratory minute volume} \times \text{concentration of CO in air} \times t$$

A constant percentage (k) of the carbon monoxide inhaled will be absorbed by the circulating blood The value for k in healthy men lies between 45 and 50 per cent. If the blood saturated with carbon monoxide contains 20 volumes per cent, then the total possible uptake by the body is one-fifth the blood volume in cubic centimeters. The percentage of car-

survival is possible for a period of several hours; at 25 to 30 C. the rectal temperature tends to become stabilized at 35 to 36 C. and prolonged survival is possible A watertight suit worn over regular clothing has been not only practical but effective in retarding loss of body heat by providing an insulating layer of air around the body.

In deep-sea diving operations, such as the salvage of the U S S "Squalus," the water may be so cold that it hampers the activity of the unprotected diver and may incapacitate him completely. Since during certain stages of the decompression he is surrounded by oxygen, the problem of supplying heat was a formidable one and involved the risk of cremating the diver should the oxygen ignite By enveloping a copper heating wire in glass cloth it was possible to overcome the fire hazard, so that divers can now work effectively in relatively cold water.

Motion Sickness

Little is known of the mechanism underlying motion sickness. In the selection of candidates for resistance to motion sickness, previous history of susceptibility to changes in motion in swings, automobiles, and trains is the most important aid It is highly probable that candidates with a positive history will also be susceptible to sea (63) and air sickness In a group of men in the U. S Navy surveyed for seasickness, a significant finding, in addition to the history, was the increase in body sway for the sick group as compared with the control group.

The chief contribution of motion sickness studies is the incontrovertible proof that hyoscine, well known for its preventive and curative effects on seasickness, affords as good or better protection than any other drug or combination of drugs (belladonna alkaloids, methedrine, chloretone, and various barbiturates) In a carefully controlled study (64), 40 cadets (7 5 per cent) became air sick on 531 flights In 200 flights in which 0 6 mg hyoscine was administered orally 30 to 60 minutes before flight, only 1 cadet (0.5 per cent) became sick The side effects from the drug were negligible, so that no fear was entertained with respect to comfort and maintenance of efficiency The effect of repeated administration of the drug was not studied

Carbon Monoxide Hazard

The difficulty of completely eliminating carbon monoxide from the air within aircraft cockpits, especially those of fighter planes in which the pilot actually is riding an internal combustion engine, presents the old problem

which entailed, in addition to isolation, foggy weather, and poor living conditions, the ever imminent possibility of death by immersion in icy water exemplifies the factors productive of neurotic fatigue. "Staleness" due to the absence of the stimulus of combat victory was also contributory.

The signs and symptoms of operation fatigue are presented in Table VIII.

Periodic rest and recreation periods, preferably on the mainland, and definite tenure of duty serve to prevent or to allay the symptoms of combat

TABLE VIII

IMPAIRMENT PRODUCED BY UNCOMPENSATED OR PROLONGED STRESSES ENCOUNTERED IN THE MILITARY ENVIRONMENT (77)

Impairment of intellectual functions	Impairment referable to somatic systems or regions			Affective behavior
	System or region	Overt	Covert	
Difficulty in thinking, concentration	Cephalic	Drowsiness	Heavy head, headache	Anxiety Tension Irritability Exaggerated fears
Impaired memory, insight, judgment	Respiratory	Shortness of breath Shallow, rapid breathing	Feeling of suffocation	Depression Lethargy
Fixation of ideas	Vasomotor	Sweating Pallor Rapid pulse rate	Weakness	Euphoria Excitement Hilarity Pugnacity
	Cardiac	Decreased ability to work Rise in diastolic pressure	Precordial distress and pain	
	Gastric		Loss of appetite Distress Nausea	
	Intestinal	Diarrhea		
	Neuromuscular	Impaired coordination Tremors Speech disturbances	Feeling of abdominal inflation Easy fatigability Malaise	

boxyhemoglobin attained during the course of carbon monoxide inhalation may then be expressed as:

$$\text{per cent COHb} = \frac{10 \times \text{minute volume} \times \text{parts CO}/10{,}000 \times t \times k}{(\text{blood volume})/5}$$

or, where k equals 0 48 and the blood volume is 6,000 cc.:

$$\text{per cent COHb} = \frac{\text{minute volume} \times \text{parts CO}/10{,}000 \times t}{250}$$

The value of k is of special interest, since it represents the fraction of carbon monoxide removed from each breath of air containing carbon monoxide. In graphic form, the slope of the line (Fig 10) is proportional to the value of k. A steep slope of the line indicates a high absorption of carbon monoxide from inhaled air. It would appear profitable to determine k values for various types of pulmonary disease

Fatigue State (73) and Psychiatric Aspects of Aviation Medicine (74–76) and Deep Sea Diving (77)

The various stresses of unaccustomed motion, extremes of temperature, anoxia, decompression sickness, the malaise of subclinical bends, and exertion tend to produce physiologic derangement which, because of compensatory effort exerted by the individual, are seldom reflected in decreased efficiency until a "breakdown" occurs For example, individuals subjected to high temperatures are able, by extra effort, to make consistently "normal" scores in psychomotor tests up to the point of collapse This was also illustrated by meticulous psychomotor testing of individuals subjected daily to 10,000 feet in the low pressure chamber for 6 hours. The tests revealed no change other than a slight reduction in the dynamic visual field, although the investigators subjectively observed a falling off in their own ability to administer the tests as a result of the repeated exposures. The chemical detection of the metabolic end products associated with muscular exertion and fatigue may offer some promise as a test for fatigue (78) However, because rapid recovery is possible, true physical fatigue may be considered of relatively minor importance

Of great importance and perhaps the chief medical problem of World War II was operation or combat fatigue (aeroneurosis) engendered not only by actual combat and the stresses enumerated but also by chronic anxiety arising from such environmental factors as inclement weather, monotonous living under poor conditions, lack of recreation and uncertainty as to tenure of duty Prolonged duty in areas like the Aleutians

Air Evacuation and Transport of the Sick and Injured

Evacuation of the injured from the scene of action by airplane and subsequent transport from hospital ship or regional hospital to large, fully equipped base hospitals and even back to the United States has been one of the outstanding achievements of the war. It mattered little whether the scene was in Europe before our foothold was secure enough to establish large hospitals, in the Burmese jungle, or on an island of the Southwest Pacific, the injured were picked up and removed to a safe place where good hospital care was available even though it was several hundred miles removed from the site of action. The Allied Forces transported 700,000 sick and wounded patients during 1942 to 1944, and the death rate in flight was only 7 per 100,000 patient trips.

Flight nurses and medical technicians rendered the same type of care as might be had in the sick bay or a first-aid battalion station on the ground. Because of the smoothness of flight as compared with ambulance travel over rough terrain, many procedures, such as bandaging, splinting, and giving transfusions of blood or serum, well-nigh impossible in an ambulance, were carried out in transit with relative ease There were two factors peculiar to air transport which required special attention; the first was the need for oxygen, especially in the case of patients with chest wounds, and the other, the expansion of gas in the intestines (82). The problem of odors was particularly distressing in the early days, but activated charcoal absorption units have proved effective deodorizers (83,84).

Measures to Accelerate Convalescence of Sick and Injured Military Personnel

The program of professionally planned and directed physical and educational training for convalescents initiated by the Air Surgeon, U. S Army Air Forces, has been of tremendous importance in shortening convalescence in military hospitals and may, to some extent, revolutionize peacetime practice The objective of this program was twofold—to shorten the number of sick days and to replace the long, profitless, morale-undermining days of inactivity with purposeful training so that the men, when returned to duty, would be at least as good or better physically and have greater proficiency in their specialties than before entering the hospital. A graduated system of calisthenics and corrective exercises and an educational program (map reading, plane recognition, etc) were begun in bed several days after surgery or as soon as temperature was normal following infection (85,86)

As an example of what may be expected in many instances, the excellent

fatigue The attitude of the Medical Officer toward these patients is wholly different from that of the civilian psychiatrist in his contact with psychopathic patients. It is accepted generally that every man has his price in his ability to "take it" and that stability of personality can be interpreted only in the light of the degree of stress imposed upon an individual

Unfortunately, there are no selection procedures yet validated which will predict psychologic fitness for combat. Data are not yet available from the Navy to compare the results of selection procedures for flight training with operational and combat performance. Certain training procedures, such as the submarine escape drill, anoxia tolerance tests at 18,000 feet, or confinement in small chambers (sometimes without light), have been of value in eliminating unfit individuals by eliciting some of the symptoms in the table above.

Protection against Flak and Crash Casualties

After considerable study and statistical analysis of causes of war wounds, their anatomic location, and the percentage of incidence for each type of plane, the Army Air Forces provided body armor, including helmets, for air crews. This reduced casualties from flak wounds by about 80 per cent.

Similar analyses are being made with reference to crash injuries, to determine the relationship between structural design and type of injury produced (80). Sometimes, in an aircraft almost completely demolished by impact forces, the human body may escape injury. On the other hand, the body may be crushed under conditions in which the fuselage is relatively intact It also happens that in some crashes one or two of the crew will be killed while the others are virtually unharmed At present, we are at a loss to explain these apparent incongruities Perhaps there are no more important investigations, not only to aviation but to all fields of locomotion, than the surveys being conducted by the Safety Bureau of the Civil Aeronautics Board and the parallel studies being made by the military services. Some of the principles underlying the use of safety belts, safety harnesses, and the redesigning of cockpits may be applicable to automobiles and may be effectual in reducing the accident rate

Another example of the type of engineering–medical investigation in progress is a study of principles and methods underlying the protection of personnel and fine instruments against the tremendous explosive forces transmitted through the steel hulls and decks of ships (solid blast) and capable of producing comminuted fractures of the bones in the lower extremities of unprotected individuals (81).

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results obtained in 600 patients with atypical pneumonia may be cited. The patients were divided into 2 groups. In the first, the patients were encouraged to get up 48 hours after their temperatures reached normal. Their stay in the hospital averaged 45 days and the relapse rate was 30 per cent. The second group were allowed to remain in bed, on an average, 8 days longer, but the exercise and educational program was instituted while they were in bed. As a result, the average stay in the hospital of these patients was 31 days, a saving of 2 weeks working time per patient, and the recurrence admission rate was only 3 per cent, or one-tenth that of the first group.

There is much in this program which warrants the attention of the medical staffs of civilian hospitals.*

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vegetations of this disease were found on necropsy. It is believed (5) that in these patients the bacterial stage escaped observation because recovery from the valvular infection occurred after a very brief clinical course, a hypothesis based upon the fact that there are exceedingly few embolic glomerular lesions, often difficult to find, and all completely healed and hyalinized. One-third of these cases developed diffuse glomerulonephritis, probably shortly after they became bacteria-free, and they ultimately died of chronic renal insufficiency.

Sulfonamide Therapy

Although cases of subacute bacterial endocarditis probably comprise only a fraction of all septic conditions, the refractoriness of the disease to any form of therapy stimulated great interest in the use of sulfonamides. Numerous clinical trials were made, using in succession prontosil, neoprontosil, sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. The number of apparent recoveries were few. When it became evident that sulfonamides alone were seldom effective, adjuvant forms of therapy were introduced. First among these was heparin. Kelson and White (6) used it in conjunction with sulfonamides in the treatment of 7 cases, only 1 was alive 5 years later. One other patient was considered as an apparent cure, although he subsequently died of active rheumatic heart disease. Simultaneously, Friedman, Hamburger, and Katz (7) used heparin alone in the treatment of 1 case without beneficial effect The rationale for the use of heparin in conjunction with chemotherapy is discussed on page 334 However, the addition of heparin to sulfonamide treatment did not produce a very significant increase in the number of apparent recoveries.

Following White and Parker's (8) observations that, *in vitro*, sulfonamides were more effective against bacteria when incubated at higher temperatures (39 C.) for a number of hours, Solomon (9) introduced hyperthermia as an adjuvant to sulfonamide therapy of bacterial endocarditis. He used typhoid-paratyphoid vaccine by continuous intravenous drip in order to maintain a temperature of about 104 F , and recorded 4 apparent recoveries of from 2 to 18 months duration at the time his report was published. Independently, Bierman and Baehr (10) used hyperthermia in combination with sulfonamides in 15 cases, and achieved sterilization of the blood stream and recovery in 2 cases Solomon (11) reported 5 apparent

Shortly before the introduction of penicillin, Lichtman (4) reviewed the results in the treatment of bacterial endocarditis with various forms of

Penicillin Treatment of Subacute Bacterial Endocarditis

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Introduction

The incidence of subacute bacterial endocarditis is unknown and it is doubtful whether an accurate idea of the frequency of this disease can be obtained from the necropsy statistics of hospitals Laws and Levine (1) found that it was the cause of death in 29 per cent of 148 cases of rheumatic heart disease, while Libman and Friedberg (2) state that it probably occurs in from 10 to 20 per cent of the cases of rheumatic heart disease. Although other investigators do not concur with this high estimate, the successful therapy of such a relatively frequent disease by means of the newer antibiotics represents a significant medical achievement.

Prior to the advent of sulfonamide therapy, the prognosis for patients with subacute bacterial endocarditis and bacteremia was hopeless except for the very slight chance of an occasional spontaneous recovery. There has been much speculation concerning the incidence of spontaneous recovery in this disease. Accurate statistics are unavailable. Judging from such information as can be gathered from the literature, the incidence is extremely low, and it is doubtful whether the frequently quoted figure of 1 to 3 per cent is not too high. Libman and Friedberg (2) state that about 3 per cent of patients may recover spontaneously. Kelson and White (3) examined the records of 250 patients from 1927 to 1939, and found that all of the 246 which they were able to trace had died. They report only one instance of questionable healing in a patient who finally succumbed to rheumatic myocarditis. Lichtman (4) in a report on the results of sulfonamide therapy in 1943, reviewed the literature on spontaneous recoveries and found only 25 instances out of a total of 2,596 cases, an incidence of 1 per cent. In the group he collected there were several series totaling as many as 815 cases without a single spontaneous recovery.

These reports ignore a group of patients described by Harbitz (2a) and Libman (2b), with all the clinical manifestations of subacute bacterial endocarditis except demonstrable bacteremia, in whom healed and calcified

pulmonary artery, successful closure was not achieved and the patient died 4 days later. At autopsy vegetations were found on the pulmonary orifice of the ductus and extending downward on the wall of the pulmonary artery The investigators stated their belief that operative procedures could succeed only when the vegetations were confined to the ductus and its immediate vicinity. Despite this failure, in 1940 Touroff and Vesell (15), guided by the pioneer work of Gross and Hubbard (16) who had successfully ligated a noninfected ductus, reported the first successful surgical ligation, with prompt recovery from the endarteritis It is noteworthy that a similar successful ligation had been performed earlier by Keele and Tubbs (17) in England in a case of Hemophilus influenzae endarteritis The mechanism by which ligation leads to healing of subacute endarteritis of a patent ductus has been fully discussed by Touroff (18) Since these first reports, there have been many other apparent cures both with and without sulfonamide therapy

As mentioned before, Kelson (13) collected 24 instances of apparent recovery from endarteritis of a patent ductus, 7 of this group of cases were treated by sulfonamides alone, while 17 were cured by surgical ligation; 5 of these received sulfonamide therapy in addition It is apparent that the operative technic has progressed sufficiently to make closure of a patent ductus a relatively safe procedure Bullock, Jones, and Dolley (19) treated 11 patients with noninfected patent ductus and obtained successful closure in 10 The patient with an infected patent ductus apparently does not present a much greater surgical hazard than one whose ductus is uninfected. Although, in these cases, recovery may now be anticipated with the use of penicillin alone, this does not obviate the need for surgical ligation of the ductus to prevent recurrence

Introduction of Penicillin Therapy

Sulfonamide therapy did not alter materially the discouraging prospect for patients suffering from bacterial endocarditis Nevertheless, sulfonamides, with and without heparin, continued to be tried, since the occasional remissions obtained certainly warranted further efforts. Somewhat more frequent recoveries were observed after massive toxic doses of the sulfonamides were employed No doubt more extensive investigations would have been tried were it not for the appearance of penicillin

Following the preliminary *in vitro* studies by Abraham *et al* (20) of the effect of penicillin upon Streptococcus viridans, Florey and Florey (21) made the first attempt to treat a case of subacute bacterial endocarditis with penicillin in 1943 The infecting organism was Str. viridans, and it

therapy He found only 21 recoveries out of a total of 489 cases treated by sulfonamides alone, a recovery rate of 4 per cent. Of 109 cases treated by chemotherapy plus heparin or hyperthermia, only 7 recovered. Of a grand total of 704 patients treated with sulfonamides with or without all forms of combined therapy, only 39 recovered or 5.5 per cent. White, Matthews, and Evans (12) who from 1939 to 1944 treated 88 cases with sulfonamides, with or without heparin, reported only 5 apparent recoveries, that is, *5.7 per cent, a remarkable similarity to Lichtman's findings with* a much larger series. In 1945; Kelson (13) collected all the reported apparent recoveries since 1939. Excluding the cases of subacute bacterial endarteritis superimposed upon a patent ductus arteriosus, he found only 38 cases, to which he added 10 of his own He does not state the total *number of cases which he reviewed, but we presume that his collected cases* correspond with those reported by Lichtman (4), and hence, represent no more than the 5 5 per cent rate of recoveries reported by the latter. Thus, the most optimistic expectations for successful therapy of subacute bacterial endocarditis following the introduction of sulfonamides did not exceed 6 per cent. Because of the hopeless outlook in this disease, one may justifiably assume that many more trials of sulfonamide therapy were made than reported, so that the number of failures was probably even greater

Treatment of Subacute Bacterial Endarteritis of a Patent Ductus Arteriosus

Recoveries from bacterial endarteritis of a patent ductus arteriosus are frequently included with reports of apparent recovery from bacterial endocarditis The clinical course of the two conditions is identical, but recent successes achieved in the former by surgical intervention are more comparable to the successful eradication of an infected focus in other septic conditions, as, for example, in jugular vein thrombophlebitis This probably accounts for the relative frequency with which patients with endarteritis of a patent ductus recover For example, Kelson and White (3) found 5 cases of infected ductus in a total of 250 instances of bacterial endocarditis, an incidence of 2 per cent, whereas in the 78 apparent recoveries from bacterial endocarditis collected by Kelson (13), in a 5 year period 24 represented cases of subacute bacterial endarteritis of a patent ductus, a recovery rate of a little over 30 per cent

The first attempt to obliterate a patent ductus arteriosus *in a patient* with subacute endarteritis was made in 1938 by Graybiel, Strieder, and Boyer (14) Because of strong adhesions between the ductus and the right

groups of investigators have contributed (24–34). Extensive clinical experience and laboratory controls in the administration of penicillin in various infections have also contributed materially to a better understanding of its use in bacterial endocarditis

Present Status of Penicillin Therapy

The need for early diagnosis and treatment of the disease in order to obviate progressive damage to the heart valves has been emphasized repeatedly. However, to be successful, treatment must be adequate. A careful analysis of the successes and failures of penicillin therapy in subacute bacterial endocarditis, as well as in other infections, indicates that certain principles are of great importance for the proper administration of this effective chemotherapeutic agent. Since the primary focus of infection in bacterial endocarditis is not amenable to surgery, it is not enough to sterilize the blood stream, we must also make certain that the valvular lesions are sterilized Several significant factors—the penicillin resistance of the infecting organism, the dosage to be used, the most effective route of administration, and the duration of therapy—must be considered if treatment is to be successful. A proper evaluation of these factors in the use of penicillin in subacute bacterial endocarditis offers the best safeguard against failures in therapy and recurrences of the disease

The Infecting Organism and Determination of Its Penicillin Sensitivity

The organism pre-eminently identified with subacute bacterial endocarditis is the Streptococcus viridans The possible value of penicillin in the treatment of this disease was soon recognized when Chain and his co-workers (35) followed by Abraham and his group (20) demonstrated that the organism was inhibited *in vitro* by the drug A variation was noted in the sensitivity of several strains to penicillin. This was subsequently confirmed by the more extensive studies of Hobby, Meyer, and Chaffee (36) and Dawson, Hobby, and Lipman (37) The latter examined 50 strains of bacteria isolated from cases of subacute bacterial endocarditis and found a variation in penicillin sensitivity from $^1/_2$ to 64 times as great as their test organism, Streptococcus haemolyticus, which is stated by them to be about $^1/_2$ to $^1/_8$ as sensitive as the strain of Staphylococcus aureus found in human infections

Keefer *et al.* (22) noted that some strains of Str viridans were more susceptible to penicillin than were others, and indicated that the course of bacterial endocarditis caused by sensitive organisms may be influenced favor-

was found to be inhibited by penicillin. Although the patient showed moderate clinical improvement for a time and repeated blood cultures during therapy were sterile, the drug was discontinued after treatment for 18 days. Shortly thereafter, the organism reappeared in the blood and the patient finally succumbed to the disease. It is interesting that these investigators reported the development of a considerable resistance to penicillin by the causative organism and suggested that it would have been better to give very large doses initially to avoid an increase in penicillin resistance. They concluded that this case gave no grounds for belief that penicillin would cure subacute bacterial endocarditis.

The second report on the treatment of this disease with penicillin appeared in this country. Keefer *et al.* (22) reported the treatment of a small series of cases, as a pilot experiment, because of the limited supply of the drug. If the results were not promising, the experiment was to be discontinued pending the availability of larger quantities of penicillin. Of the 17 patients treated, 10 were unaffected by the drug in the amounts used, 4 died, and only 3 showed temporary improvement while under treatment; two of the latter relapsed as soon as therapy was discontinued. The total amounts of penicillin used varied from 240,000 to 1,760,000 units and the drug was given over periods ranging from 9 to 26 days Some strains of the infecting organism (Str viridans) were more susceptible to the drug than others, and in some instances temporary sterilization of the blood stream was achieved. Their report concludes with the statement that some of these infections with susceptible strains of organisms might possibly be favorably influenced if treatment were started early in the course of the disease and carried on intensively

Shortly following these unfavorable experiences, the first successful treatment of subacute bacterial endocarditis with penicillin was reported by Loewe *et al* (23). These investigators used heparin in combination with penicillin; their 7 patients received from 1 to 4 courses of therapy, the total amounts of penicillin varying from 867,920 to 7,890,340 units, and remissions were obtained in all This optimistic report soon stimulated other attempts. At the same time, the Committee on Chemotherapeutics and Other Agents, under the aegis of the National Research Council, encouraged further study by releasing supplies from the limited stocks of penicillin then available to various groups of investigators Ever-increasing numbers of apparent recoveries were soon added to the first small group treated by Loewe and his co-workers

At the present time the treatment of subacute bacterial endocarditis with penicillin rests upon a foundation of wide experience to which many

the efficacy of penicillin in the treatment of infections, a dosage schedule producing a blood level at least equal to, and preferably 5 times greater than, that necessary to inhibit the organism *in vitro* is of prime importance.

Many methods have been devised for testing the penicillin sensitivity of bacteria The organisms most commonly used as a standard are strains of Str. haemolyticus and Staph aureus. The method introduced by Fleming in 1929 was that of the serial dilution of the drug in bacterial broth to which the same volume of the bacterial suspension was added. Inhibition of the organism was then observed in terms of opacity of the broth after varying periods of culture Since then many other equally good methods have been reported. At the present time no one method enjoys great superiority over the others Some of the methods can be applied only by specially trained laboratory technicians (60); others are simple, such as that described by Cooke (39), and can be readily introduced into any small laboratory It would be desirable if some standard reference of organism resistance would prevail The term "coefficient of resistance" was introduced (32) to indicate the relative penicillin sensitivity of an organism as compared to a standard test strain, using Heatley's Staph. aureus strain. A concentration of approximately 1,000 organisms per cc of culture medium was obtained by serial dilution of a turbidimetrically standardized 18 hour old culture It required 0 04 units of penicillin per cc. to inhibit the organisms The resistance of the infecting organism is expressed as a factor of the penicillin sensitivity of the standard, and this factor is termed the coefficient of resistance

Although no hard and fast rule can be established, numerous experiences with subacute bacterial endocarditis and other infections permit certain statements to be made with respect to the relation between dosage to be used and resistance of the infecting organism Keefer maintained that a minimum blood level of 0 16 to 0 20 units of penicillin per cc of serum must be achieved in order to treat a patient infected with Staph. aureus, and other investigators have confirmed his observation A guide to minimum dosage, in terms of the infecting organism's resistance, is listed in Table I, but higher levels are desirable (see page 323)

In many instances large doses without a corollary determination of the sensitivity of the infecting organism may prove effective Occasionally, what may appear to be a large dose may well be inadequate. This is best illustrated by the following experience of the authors a case of enterococcic subacute bacterial endocarditis in which the organism exhibited a resistance to penicillin 150 times that of the test organism, which was strain H of Staphylococcus aureus, required a minimum daily dose of

ably if treatment is started early. Similarly, a variation in strain susceptibility was noted in the first group of successfully treated cases reported by Loewe *et al.* (23). The bacteria were sensitive to dilutions of 0 007 to 0 01 units of penicillin per cc. Dawson and Hunter (24) found a strain variation in penicillin resistance from 1 to 16 times that of the test organisms (Str. haemolyticus) in 20 cases of bacterial endocarditis treated by them Three cases were rejected for treatment because the infecting organisms had a penicillin resistance from 160 to 800 times that of the test organism. Many other investigators have reported wide variations in penicillin sensitivity of the group of streptococci found in bacterial endocarditis, namely, Str. viridans, Str. faecalis (Enterococcus) and nonhemolytic or gamma streptococci.

The penicillin susceptibility of the infecting organism is an important guide to the dosage to be employed in a given case The assumption of a correlation between *in vitro* sensitivity and penicillin concentration in the body fluids is warranted by numerous experiences in the treatment of various infections Bloomfield, Kirby, and Armstrong (38), analyzing the causes of failure of penicillin therapy, found good evidence that a correlation exists between bacterial sensitivity *in vitro* and the patient's clinical response One of their patients who was treated with 450,000 units of penicillin daily failed to respond; the infecting organism was shown to be insensitive to high concentrations of the drug *in vitro* Meads, Harris, and Finland (26) noted that patients with subacute bacterial endocarditis responded more rapidly to therapy when the penicillin dosage was so adjusted that a higher penicillin blood level was maintained than that necessary to inhibit growth of the infecting organism *in vitro* In 25 cases of subacute bacterial endocarditis, it was found (32) that there was a variation in strain resistance of the infecting organisms varying from 1 to 25 times that of their test organism Although other factors must be taken into consideration, a correlation existed between the *in vitro* resistance of the infecting organism and the dosage of penicillin to be administered

Preliminary dosage schedules for the treatment of infections were introduced by the Oxford group mainly on the basis of their experience with Staphylococcus aureus and Str haemolyticus The short range of penicillin sensitivity that is shown by these organisms is in decided contrast to the wide variation noted in the bacteria isolated from cases of subacute bacterial endocarditis (37) The unfavorable results obtained shortly following the introduction of penicillin may in part have been due to dosages that were inadequate to overcome the resistance of the infecting organism With due regard for the importance of the many other factors contributing to

therapy. Certain facts suggest, however, that this may not always be necessary." Nonetheless, from the early reports on penicillin treatment of subacute bacterial endocarditis it appears that the drug was given by the continued intravenous method in most instances, and that occasionally, because of difficulties with the former, intermittent intramuscular injections of the drug were substituted

Many difficulties were encountered with the continuous intravenous method of administration Chief among these was the frequent occurrence of thrombophlebitis at the site of injection. In addition, obstruction of the needle necessitated frequent changes of the intravenous drip, and local infiltration often ruined the veins. In many instances, administration proved extremely difficult The use of heparin, although it diminished the tendency to thrombophlebitis, did not completely obviate this complication. Certain refinements, such as the use of smaller gage needles with a slow drip and frequent changes in the site of the needle, also aided in reducing the incidence of thrombophlebitis

In order to avoid the difficulties of continuous intravenous administration, the continuous intramuscular administration of the drug was introduced by Harris (41) in this country and by Last (42) in England. It was found that the blood levels obtained by this method were about equal to those following continuous intravenous infusion with similar daily quantities of drug In addition, smaller volumes of fluid could be employed, the drip usually running at the rate of about 8 to 10 drops per minute Pain at the site of intramuscular infiltration, as well as edema of the injected extremity, were complications not infrequently encountered. However, this method is of value when the presence of thrombophlebitis prohibits the use of the intravenous route

Undoubtedly, maintenance of a constant blood level of penicillin is highly desirable At present, the only means by which this can be achieved effectively is through the continuous intravenous or intramuscular routes. The disadvantages of both these methods are not very significant in the treatment of acute infections, where therapy is of relatively short duration. However, in subacute bacterial endocarditis, in which penicillin administration is usually continued for 4 weeks or more, the cumbersomeness of these methods, as well as the complications that often ensue, tend to interfere with therapy Furthermore, with a continuous intravenous infusion, the daily injection of 1,500 to 2,000 cubic centimeters of fluid may be required; in the occasional cases with a tendency to heart failure, the use of such quantities of solution may be interdicted.

Even in the initial treatment of subacute bacterial endocarditis with

TABLE I

SCHEDULE OF INTRAMUSCULAR PENICILLIN THERAPY IN TERMS OF ORGANISM RESISTANCE

Penicillin resistance of infecting organism*	Units of penicillin required every 3 hours	Peak blood level obtained†	Minimal blood level required‡
1	15,000	0 5	0 2
2 to 3	25,000	1 0	0 6
4 to 5	50,000	2 0	1 0
5 to 10	100,000	6 0	2 0
10 to 20	200,000	11 0	4 0
20 to 30	300,000	16 0	6 0

* These figures represent the factors obtained by comparing the penicillin sensitivity of the infecting organism with a standard test strain of Staphylococcus aureus H of the Oxford group of investigators

† Expressed in units per cc of blood serum obtained 20 minutes after intramuscular injection of the drug

‡ Amount of penicillin, in units per cc. of blood serum, constantly present in the blood stream.

8,000,000 units to produce a sufficient blood concentration to meet the infecting organism's resistance Although such cases are uncommon, the marked variation in the sensitivity of the various strains of bacteria encountered in subacute bacterial endocarditis requires an accurate penicillin sensitivity determination in every instance.

Methods of Administration and Dose of Penicillin

At the present time penicillin must still be given parenterally in the majority of infections. Although both the intramuscular and intravenous routes offer certain disadvantages, one or the other must suffice until more suitable methods have been found In spite of the satisfactory results obtained in the treatment of many infections by using the intramuscular route alone, with intermittent injections at 3 or 4 hour intervals, the tendency at the outset was to use the continuous intravenous drip in the more severe infections This was particularly true in the treatment of subacute bacterial endocarditis The presumptive purpose was to maintain a constant level of the drug in the blood stream, although there was no conclusive evidence that this was a prerequisite for the adequate treatment of the disease. Dawson and Hobby (40) point out that little was known concerning the minimal effective concentration of penicillin for various types of infection They state. "*Such experimental work as has been done* has been based on the assumption that effective concentrations should be constantly maintained in the circulating blood as is the custom in sulfonamide

mate blood concentrations of penicillin which are obtained by the administration of varying daily doses by continuous intravenous infusion. A comparison of the two tables demonstrates that when comparable total daily doses are used, the constant blood level obtained by the continuous intravenous method is maintained only for about 1 to 2 hours after each intermittent intramuscular injection However, the favorable results achieved by the use of the latter method, both in acute infections as well as in bacterial endocarditis, would seem to indicate that this is not necessarily a barrier to effective therapy. Although logically it would seem that the exposure of the infecting organism to a constant effective concentration of penicillin in the body is likely to be more beneficial, in practice good results may also be obtained when the exposure is intermittent, provided the intervals are not too long. Exactly how long an interval between injections, hence between effective blood concentrations, may be allowed probably depends upon the nature and resistance of the infecting organism, the location *of the infection, the resistance of the host, the dose of drug, and other factors* For example, effective therapy of pneumococcic pneumonia has been reported with the use of 4 daily injections of penicillin at intervals of 4 hours, and a free nocturnal interval of 8 hours Several cases of bacterial endocarditis were treated (32) with intramuscular injections every 6 hours for 4 weeks, with apparent remission; this interval, however, is not recommended for routine use.

TABLE III

PENICILLIN BLOOD LEVEL OBTAINED BY CONTINUOUS INTRAVENOUS INFUSION

Total daily dose, units penicillin	Average range of blood level, units per cc of blood serum*
100,000	0 1 to 0 2
200,000	0 2 to 0 4
500,000	0 8 to 1 2

* Figures represent an average of at least 10 series of determinations, with from 2 to 5 determinations in each series

The value of the intermittent intramuscular injection of penicillin lies not only in the convenience to the patient and physician but also in the simplified administration of the drug and the absence of complications There are also many instances in which infections by bacteria with an unusually high degree of penicillin resistance may require a blood level unattainable by continuous intravenous drip but readily achieved intermittently throughout the day by intramuscular injection For example, an

penicillin occasional experiences indicated that intermittent intramuscular therapy, every 3 or 4 hours, might be effective. As a rule, the total daily dose deemed necessary for continuous intravenous administration was divided into 6 or 8 single doses and injected intramuscularly every 3 hours. This method subsequently became more popular because of the disadvantages of the continuous intravenous or intramuscular infusion. A number of workers (26,32) employed intermittent intramuscular therapy every 3 hours or less, as the method of choice and noted as good results as those reported with continuous intravenous therapy.

Objection has been raised to the use of intermittent intramuscular therapy on the grounds that the penicillin concentration in the blood reaches a high peak shortly after injection and then falls rapidly, so that there are intervals of 1 or 2 hours during which an effective concentration may not be present in the blood stream. Table II gives the rise and fall of the penicillin blood level after a single intramuscular injection of varying doses of the drug. These figures correspond closely with those obtained by Fleming et al (43), and by McAdam, Duguid, and Challinor (44). It might be mentioned that occasional discrepancies were encountered, in that the maximum level failed to reach the anticipated peak following the injection of varying doses. No adequate explanation could be offered for these discrepancies. For comparison, there are listed in Table III the approxi-

TABLE II

PENICILLIN BLOOD LEVEL OBTAINED AFTER A SINGLE INTRAMUSCULAR INJECTION*

Penicillin units injected	Units per cc of blood serum after injection			
	After 20 min	After 40 min	After 60 min	After 120 min
15,000	0.5	0.2	0.14	Trace
20,000	0.8		0.3	0.06
25,000	1.0	0.8	0.6	0.1
30,000	1.3		0.8	0.13
40,000	2.0	1.3	1.0	0.4
50,000	2.0	1.5	1.3	0.6
100,000	6.6	4.0	2.5	1.0
200,000	11.4	6.6	4.3	1.2
300,000	16.0	13.0	9.5	2.3

* These figures represent the average only of at least 25 series of determinations, with from 3 to 6 determinations in each series. The variations in some instances were marked, but on the whole the averages represent a fair picture of the blood level which may be anticipated with the various doses employed.

5 per cent glucose solution was established; every 3 hours the glucose solution was emptied from the container and from 700,000 to 1,000,000 units of penicillin, dissolved in from 30 to 40 cc. of distilled water, were introduced and allowed to enter the blood stream rapidly. This was followed by the slower continued infusion of glucose solution during the intervals, thereby obviating the need for single intravenous injections every 3 hours. By this method, blood levels of from 108 to 133 units of penicillin per cc. of serum were obtained. The peak blood level, however, lasted only 10 minutes and dropped off very rapidly, as is known to occur after intravenous injections. Intermittent intravenous infusion of the drug was alternated with intermittent intramuscular injections, for although the drug was given only once every 3 hours intravenously, thrombophlebitis ensued nevertheless. With this technic, the patient was treated for 5 weeks and effective sterilization of the blood was achieved during the period of therapy. Since then the bacteremia has recurred, indicating that the vegetations had not been completely sterilized. This combined method might perhaps be of value for the continued treatment of other infections caused by very resistant bacteria.

Until recently, the parenteral route of administration was thought to be the only method that could be used for penicillin therapy, the destruction of penicillin by gastric secretions, as was demonstrated in earlier studies, preventing the use of the oral route. Many reports have now appeared in the literature on penicillin given in combination with various substances calculated to neutralize the destructive effect of the gastric juices. A number of adjuvants seem to be promising, among them trisodium citrate (45), basic aluminum aminoacetate (46), corn oil and lanolin (47), human plasma protein (48), raw egg white and sodium bicarbonate (49), aluminum hydroxide (50,51). However, the blood levels obtained after ingestion reach only about $^1/_3$ to $^1/_5$ that obtained by the intramuscular route. It appears that this ratio holds even when unbuffered penicillin is taken by mouth. Recently, Finland, Meads, and Ory (52) found that the oral administration of penicillin in normal saline resulted in blood levels as high as those obtained when the drug was used with buffer salts. The penicillin saline solution was given before and after meals with identical results. Simultaneously, Bunn *et al* (53) treated pneumococcic pneumonia patients with penicillin administered orally and obtained equally satisfactory therapeutic results whether the penicillin was given as a suspension in oil, or as the plain powder dissolved in water or enclosed in a gelatin capsule. Since, as a rule, much higher blood levels are needed for the treatment of subacute bacterial endocarditis, the oral administration of

organism with a coefficient of resistance of 100 can be inhibited by a penicillin blood concentration of about 20 to 30 units per cc. of serum (interpolated from Table I). For such a level, a daily intravenous dose of 10,000,000 to 15,000,000 units of penicillin would be required (interpolated from Table III), an amount that might be impossible to administer because of the phlebitis induced by such a high concentration of the drug Since high peaks are obtained, albeit for short periods, after single intramuscular injections, a blood level of 30 units of penicillin per cc. could be achieved after each injection of about 600,000 units of drug. As many as 8 such injections a day could be tolerated for weeks, and it might be anticipated that this schedule of therapy would be effective. The correctness of this assumption has been borne out in the authors' experience. In one instance a case of actinomycosis was treated with only 2 daily intramuscular injections, each of 200,000 units, supplemented by an additional injection of 100,000 units into the granuloma located in the chest wall. The organism had a coefficient of resistance of 50, and therefore required a blood level of 10 to 15 units of penicillin per cc. of serum. Concentrations of 11.4 units per cc of blood serum were obtained by injecting 200,000 units intramuscularly, and 17 units per cc after the 300,000 unit dose Treatment was continued for 5 weeks, with marked regression of the granuloma and the accompanying pleuritis and pneumonitis. Such long intervals between injections are possible because of the slowly progressive character of actinomyces infections; acute or subacute infections, however, require more frequent treatment.

The large doses required to produce the high blood concentration necessary for an organism with a very high coefficient of resistance may be given by intermittent intramuscular injection every 3 hours This was accomplished recently in the following case The patient had subacute bacterial endocarditis due to Enterococcus, with a coefficient of resistance of 150 It would have required 15,000,000 to 22,000,000 units of penicillin daily to treat this patient by continuous intravenous infusion, a well-nigh impossible feat under present circumstances Since it was estimated that a blood level of about 45 units per cc was required, it was decided to inject 1,000,000 units every 3 hours. Blood levels of 67 to 73 units per cc were obtained The intramuscular injection of this amount of drug required the use of about 20 cc of solution Although the repeated intramuscular injections of such quantities caused much pain and fever, possibly due to the sterile abscesses produced, sterilization of the blood stream was achieved for the first time. Later, treatment was supplemented by a modified continuous intravenous drip, as follows: A continuous infusion of

In patients with subacute bacterial endocarditis, it is especially important that the dose should greatly exceed that necessary to produce a blood level adequate to match the *in vitro* resistance of the infecting bacteria. Without being wasteful of the drug, it would be desirable to achieve as high a level as is possible and compatible with ease of administration. The value of high blood levels may be twofold. In the first place, high concentrations of the drug may be bactericidal as well as bacteriostatic. Bigger (61) states:

"It is sometimes admitted that penicillin has a bactericidal action, but only in concentrations higher than are attainable in the human body. My experiments do not support this view since I have demonstrated well-marked killing power in concentrations ranging from 1 down to $^1/_{24}$ unit per cubic centimeter, while in the sera of patient undergoing treatment, such concentrations as $^1/_{16}$, $^1/_8$, and $^1/_4$ units per cubic centimeter are often, and $^1/_2$ and 1 unit per cubic centimeter occasionally, recorded"

The concentrations noted by Bigger held for the early period of penicillin therapy, but today, with the greater availability of the drug, these concentrations are easily exceeded Shwartzman (62) has demonstrated that penicillin exerts a bactericidal action, but in proportionately high concentrations. Other investigators have obtained similar results. Although the bacteriostatic action of penicillin is usually sufficient to permit the host to dispose of the offending bacteria, a bactericidal effect is highly desirable to assure sterilization of the infection.

Loewe (25) suggested a blood level about 5 times higher than that of the *in vitro* inhibiting concentration of the drug This figure is an arbitrary one, and when the organism is of high resistance certainly may not be achieved

A second possible benefit of high blood concentrations of penicillin may be in the greater penetrating power of the drug into various body tissues and fluids Struble and Bellows (63) experimentally were able to recover the drug from tissues of the dog's eye, such as the sclera, conjunctiva, and chorioretinal layer, only when doses approximately 8 times the usual clinical dose (i e , 12,800 units/Kg body weight, vs. the usual dose of 1,500) were given They found that certain organs and tissues extract large amounts of penicillin from the blood and eventually may contain a higher concentration than the plasma, suggesting that some tissues may exercise a selective absorption Their studies are of great interest, since such relatively avascular tissues as the conjunctiva and sclera showed penicillin concentrations higher than the blood The concentration in these tissues rose slowly, reaching a peak at a time when the blood level was already

penicillin is not feasible at present except perhaps for infections caused by bacteria of low resistance.

Attempts to prolong the action of the drug in man were made as soon as pharmacologic studies had demonstrated that it was rapidly excreted. Rammelkamp and Bradley (54) administered from 30 to 40 cc of diodrast to patients receiving penicillin and obtained both higher and more prolonged blood levels, together with a diminished urinary excretion of the drug. The following year Beyer *et al.* (55) employed sodium *p*-aminohippurate intravenously together with penicillin and were able to obtain a twofold increase in plasma concentration of penicillin When the concentration of the adjuvant was raised, the penicillin blood level increased fivefold. Some untoward reactions, such as nausea, flushing, and diarrhea were observed following the use of sodium *p*-aminohippurate. Bronfenbrenner and Favour (56) demonstrated a similar increase of plasma penicillin concentrations after the combined use of a fluid intake restricted to 1,500 cc. and ingestion of about 3 grams of salt, together with the oral administration of 15 grams daily of a benzoic acid suspension in sweetened acacia They noted an eightfold increase in blood penicillin levels together with a prolongation of the effective blood level Less impressive results were obtained by using adrenalin (57), and peanut oil, beeswax, and penicillin mixtures (58,59). The ultimate value of these accessory means of prolonging penicillin action as well as increasing the plasma concentration remains to be demonstrated clinically. Their use is certainly indicated in instances of high penicillin resistance of the infecting organism, when very high blood levels of penicillin must be attained Further, with more experience it might be possible to reduce the number of daily intramuscular injections needed for treatment of subacute bacterial endocarditis, thereby affording the patient much relief and making possible longer periods of therapy.

Regardless of the route of administration, there is a moderate degree of individual variation in the height of the penicillin blood level that follows a given dose of drug. Since effective therapy is predicated upon the maintenance of an optimum concentration of penicillin in the body fluids, it is necessary to check the blood levels frequently in individual cases. As pointed out in Table II (page 318), variations were noted following single intramuscular injection of a given quantity of the drug. It may be necessary on occasion to increase the dose twofold or even threefold in order to insure the desired blood level. Unless blood levels are checked frequently failure in therapy may ensue, despite the use of total daily doses of the drug apparently adequate to produce the desired optimum penicillin blood level.

known, for example, that patients with agranulocytosis continue to manifest fever and other toxic symptoms even though treated with large doses of penicillin It is not until leukocytic regeneration occurs that the symptoms disappear, although no doubt the bacteriostatic effect of the penicillin prevents unmitigated proliferation of the infecting organisms and overwhelming toxemia The role of antibiotic agents in acute infections is primarily one of retarding bacterial growth so that the opportunity is given for the host to mobilize his natural defenses. Healing of the affected tissues will then usually follow at a fairly rapid pace. However, when the primary focus is deeply situated, it may be inaccessible to penicillin. Furthermore, even though the underlying focus can be reached by the drug, the affected tissue may heal very slowly. This is particularly true of the valvular lesions in subacute bacterial endocarditis. It is evident, then, that the length of time during which the action of the antibiotic is maintained in the body is an important factor in the effective therapy of this disease.

A review of the studies on the use of penicillin in subacute bacterial endocarditis so far reported indicates wide variations in the duration of treatment. Dawson and Hunter (24) obtained remission of the disease in 5 patients treated for periods of only 10 to 14 days with doses ranging from 100,000 to 320,000 units daily On the other hand, relapse after therapy occurred in 2 patients treated for 103 and 85 days, respectively. In the latter instance, the amount of drug administered in each case was sufficient to maintain a blood level that would match the *in vitro* resistance of the infecting organism. Bloomfield, Armstrong, and Kirby (33) treated 11 cases of bacterial endocarditis for 8 weeks and concluded that the minimum period of therapy should be 2 months, or perhaps longer. Loewe (25) recommended a minimum treatment period of 5 weeks. Meads, Harris, and Finland (26) obtained recovery of 7 out of 9 cases treated by intramuscular injection every 2 hours for a period of 2 weeks. A lack of unanimity concerning the duration of penicillin therapy still prevails, although there has been a tendency to prolong treatment schedules with increasingly satisfactory results.

The present authors treated 25 cases of subacute bacterial endocarditis and, like other investigators, established an arbitrary period of treatment. It was found that in most instances, a 4 week period of penicillin administration sufficed to produce recovery from the disease However, comparable to the experience of Dawson and Hunter (24), they observed a patient infected by Streptococcus viridans, who required 120 days of treatment, although the organism was only twice as resistant to penicillin

falling. They advised larger doses of drug than were customarily being given at that time. No doubt, further observations along this line will have to be undertaken before any conclusive statement can be made with respect to the greater penetrating power of higher blood concentrations of penicillin. Nevertheless, the penetration of the drug into such relatively avascular tissues as the sclera and conjunctiva, suggest a possible parallelism to the penetration of the drug into the heart valves.

The use of so-called "booster" doses was introduced (32) in the hope of thereby facilitating penicillin penetration into the focus of infection in various conditions, as well as into the vegetations on the heart valves in bacterial endocarditis. The "booster" dose consisted of a single intramuscular injection of 50,000 to 300,000 units, twice daily, in addition to the usual therapeutic dose (15,000 to 30,000 every 3 hours). Favorable results were noted in a number of instances in which the usual dose had failed to sterilize. Since the drug is now freely available, 8 large doses, each of 100,000 units or more, would certainly seem more desirable.

While no rigid rule of dosage or route of administration is valid at the present time, particularly since many investigations with respect to both are under way, it would appear that the intramuscular injection every 3 hours of 100,000 units should prove effective in most instances. The majority of cases of subacute bacterial endocarditis are infected by organisms with a resistance to penicillin about 1 to 5 times that of the standard test strain of Staphylococcus aureus. A blood level peak of 6 6 units per cc. of serum obtained after the intramuscular injection of 100,000 units would suffice for both bacteriostatic and possible bactericidal effect (that level being about 5 times greater than needed to match the *in vitro* resistance of an organism 5 times as resistant as the Staphylococcus aureus) In addition, if high concentrations have greater penetrating power, this level might well facilitate the penetration of the drug into the vegetations on the heart valves and aid in the ultimate sterilization of this primary focus Unquestionably, a constant blood level of 6.0 or 7 0 units per cc of serum, rather than the intermittent one obtained by the spaced intramuscular injections, would be greatly desired In order to achieve this, a daily dose of 2,500,000 units is necessary, while this is certainly feasible, the complications of thrombophlebitis with high concentrations of drug is likely to prevent prolonged use of continuous intravenous therapy.

Duration of Treatment

In the final analysis, the action of antibiotics in the control of infections is only complementary to the natural defenses of the host. It is well

Clinical Response

One of the striking effects almost uniformly observed following administration of penicillin in subacute bacterial endocarditis is the marked improvement in general well being. Occasionally within 24 hours, more often after several days, the patients appear improved and state that they feel much better. There is increase in appetite and greater general responsiveness

The fever usually falls to lower levels within 24 to 72 hours and may remain slightly above normal limits throughout the remainder of the period of therapy. An occasional rise in temperature is frequently encountered and often is associated with the occurrence of embolic phenomena. At other times, it may be due to causes unrelated to the major illness, or it may be inexplicable A common experience in the early days of penicillin therapy by continuous intravenous infusion was the presence of recurrent febrile episodes This was in part accounted for by the presence of pyrogenic substances in the relatively crude drug then manufactured At times such febrile episodes herald the development of thrombophlebitis Fever rarely follows the intermittent intramuscular injection of penicillin, even though moderately large doses are used Combined therapy of penicillin and heparin often gives rise to recurrent febrile reactions which have been shown to be due to the heparin. In the uncomplicated case, the continued presence of fever should arouse a suspicion that the infection is not responding to treatment, even though the blood culture may at times be sterile Similarly, a subfebrile course may be observed, even though the organism is consistently cultured from the blood Although the favorable case, while under treatment, usually shows a return of the temperature to normal levels, a continued subfebrile course may also be observed in a patient who may ultimately achieve a permanent remission of the disease

No exact relationship exists between the presence of petechial spots and bacteremia Petechiae are often noted for a number of days after penicillin treatment is started, although blood cultures may already be sterile Usually they tend to disappear completely after the first week of treatment, and they are seldom noted after the third week The complete disappearance of petechiae is associated with healing of the valvular lesions Rarely, an occasional petechial spot may be present though repeated blood cultures are sterile. Negative blood cultures do not necessarily prove the complete absence of bacteria from the blood stream and the presence of an occasional petechial spot may be indicative of the fact that bacteria still persist in the valvular vegetations.

Gross embolic phenomena, such as infarction of the spleen or kidneys,

as the standard test strain of Staphylococcus aureus. The following explanation might possibly account for such discrepancies in response to treatment. Superficial valvular lesions are readily accessible to the penicillin circulating in the blood stream and hence the bacteria in such lesions are more easily exposed to the effects of the drug. If high concentrations of penicillin are present, a bactericidal effect may obtain so that the healing of superficial lesions is fairly rapid. It is therefore possible that such cases recover following a treatment period of only 2 weeks. But the more extensive, deeply situated valvular lesions would respond much more slowly, and unless penicillin therapy is continued until advanced healing has occurred, bacteria deeply embedded in the valvular granulations may survive and lead to early recurrence when therapy is discontinued. Hence, effective bacteriostasis must be maintained during the long period of time necessary for the repair of the relatively acellular and avascular valves.

The character and extent of the valvular lesions vary from case to case, as probably does also the rate of repair of the valves and the organization of the vegetations. The duration of the disease prior to penicillin therapy may be only one factor in the extent of the valvular disease and hence cannot be used as an index for the length of treatment. Likewise, the penicillin resistance of the infecting strain of organism, assuming adequate dosage, bears no relation to the permanency of response to therapy in a given case. There are thus no certain criteria by which the duration of therapy can be established.

Although the number of cases treated to date is not very large, they represent a fair cross section of what may be expected in the way of problems in therapy. If one excludes the earliest penicillin-treated cases, it is evident that most investigators have found a minimum period of 4 weeks and an optimum period of 8 weeks of treatment effective in most instances. However, this estimate may have to be revised in the future. A careful follow-up of the cures and recurrences will be necessary before a more uniform experience in treatment permits the establishment of an optimum period of therapy. Once again it might be emphasized that although the nontoxicity of the drug allows multiple courses of treatment, a careful evaluation of each case at the outset is essential so that adequate and effective therapy may be instituted and progressive valvular damage avoided. Inadequate dosage of penicillin with unnecessary prolongation of treatment is uneconomical and may ultimately leave the patient cured of bacterial endocarditis but doomed to chronic invalidism or to an early death from congestive heart failure.

month following cessation of therapy, for the early recurrence of infection may thus be detected. After the patient is discharged from the hospital, blood cultures should be taken at monthly intervals for 3 successive months, and thereafter the interval may gradually be increased to 3 month periods. A positive blood culture will disclose the presence of a recurrence at a time when objective signs may still be lacking.

The leukocyte count may or may not be elevated in bacterial endocarditis Careful study, however, frequently reveals a slight to moderate shift to the left even though the count is only slightly increased In the presence of complications, such as renal or splenic infarction, the leukocyte count may rise suddenly The white cell count is not a satisfactory index of the effect of therapy However, a favorable course is frequently attended by a normal white count and a diminution in the number of immature cells

The erythrocyte sedimentation rate is a good index of the response of the patient to treatment. Recovery is attended by a return of the sedimentation rate to normal, but it may not occur immediately after cessation of penicillin therapy. Several factors may account for a continued rapid sedimentation rate, such as the presence of incompletely healed infarcts, active rheumatic fever, or complications unrelated to the disease An accelerated sedimentation rate after therapy has been completed and the patient had been observed for several weeks warrants suspicion of a persistent infection on the heart valve

The majority of patients with subacute bacterial endocarditis manifest a slight to moderate anemia Although regeneration of the red cells and rise of the hemoglobin is usually slow, even when the infection has been controlled, successful therapy is usually accompanied by a return of the erythrocyte count and hemoglobin to more or less normal limits. Accessory aids such as transfusions and iron administration may be indicated at times

The degree and extent of cardiac and valvular involvement is extremely variable in subacute bacterial endocarditis Too often we are accustomed to think of this disease as being primarily one in which the heart valves alone are affected But postmortem examinations frequently reveal multiple inflammatory foci in the myocardium, and the disease must therefore be looked upon as one which effects the entire heart Hence, early and adequate therapy not only prevents progressive valvular damage but also serves to reduce injury to the heart muscle The possible complication of cardiac failure when continuous intravenous therapy is used, as previously mentioned, must be taken into consideration and the load upon the heart reduced to a minimum

are apt to occur as late as 3 or 4 weeks after treatment is started. In part, these may be due to detachment of fibrinous masses during the course of healing, but they may signal continued progressive valvular destruction. Often spikes of fever are associated with embolic phenomena, yet blood cultures taken at such times are frequently sterile Some observers have reported the presence of embolic phenomena as late as 5 weeks after the beginning of penicillin therapy. It may be conjectured that although bacteria have disappeared from the healing valve, fibrin may continue to be deposited on the organizing granulations and may subsequently be thrown off as emboli. Since such a process might continue until the vegetations are completely organized, one may anticipate the occurrence of occasional embolic manifestations as long as 8 or 10 weeks following the inception of penicillin therapy.

The bacteremia of subacute endocarditis usually responds very rapidly to the administration of penicillin. As a rule, blood cultures taken from 24 to 48 hours after the commencement of treatment are sterile and in occasional instances even after 4 to 12 hours. At times, 4 or more days may elapse before the blood stream is sterilized, assuming that an adequate dosage of the drug has been given. Patients cured by a single course of penicillin therapy usually have negative blood cultures throughout the entire treatment period. Occasional positive cultures during the course of treatment are apt to indicate ultimate failure and should lead one to re-evaluate the therapeutic program

Bloomfield, Armstrong, and Kirby (33) found no relation between the degree of bacteremia and the readiness with which the blood stream was sterilized. This has not always been the experience of other workers (32) who report that several patients with overwhelming bacteremia were encountered in whom doses of penicillin apparently adequate to produce a blood level sufficient to match the resistance of the infecting organism failed to sterilize the blood stream. Sterilization was achieved only when much higher blood levels of penicillin were attained Whether in such instances the greater concentrations of penicillin facilitated sterilization through the bactericidal effect of the drug, as previously discussed, or through enhanced penetration into the depths of the valvular infection, cannot be stated. Their experience indicates that, in the presence of marked bacteremia, consideration must be given to the use of far greater doses than those ordinarily required

Blood cultures should be taken at intervals of 1 or 2 days during the first few days of treatment, if negative, the interval may then be prolonged to 7 days. It is desirable that weekly blood cultures be taken for at least 1

However, the observations are still too limited to warrant any definite statements at the present time.

Reactions to Therapy

The remarkable qualities of penicillin reside not only in its value as an antibiotic agent against many virulent organisms but in its relative nontoxicity. There is hardly another drug which combines such low toxicity with such high therapeutic activity. It is variously estimated that the maximum dose which man can tolerate is about 20,000,000 units daily. The authors have given 10,000,000 units daily for a week with no evidence of toxicity.

Among the general toxic reactions known to be caused by the drug are cramps, sweating, flushing, headache, urticaria, angioneurotic edema, and fever. Eosinophilia has also been observed. With the improved manufacture of the drug, and its greater purity, many of the reactions noted early in the use of penicillin have diminished or disappeared. However, individual hypersensitivity still remains a factor to be considered Except for the rare occurrence of angioneurotic edema, none of the reactions following the use of the drug necessitate the discontinuation of therapy. Urticaria is the most common complication, having been noted by Lyons (64) in 5 7 per cent of the cases and by Keefer and his associates (22) in 2 8 per cent. At the present time the incidence is probably much lower Occasional instances of allergy to the drug have been reported, with all the features common to other expressions of hypersensitivity Criep (65) described the presence of precipitins and a positive passive transfer, as well as skin sensitivity to penicillin, in a dilution of 1.100 Welch and Rostenberg (66) observed a tuberculin type of hypersensitivity to crystalline penicillin sodium. It is interesting that patients showing hypersensitive reactions to penicillin are not allergic to the mold, i e., Penicillium notatum

The febrile reactions commonly encountered when the drug was first employed are seldom met with at present They were particularly frequent when penicillin was given by continuous intravenous drip and at times interfered with the proper evaluation of the patient's response to therapy Occasionaly, fever has been noted after intramuscular use of the drug

By far the most troublesome and common complication of penicillin therapy is the thrombophlebitis which occurs during continuous intravenous administration Although the impurities present in early preparations of the drug may have been a contributory cause, their reduction through

A certain amount of valvular damage will ensue in every case of bacterial endocarditis despite early and intensive therapy. The degree of damage will depend upon the extent of initial involvement and the rapidity of valve destruction. Progressive valvular destruction has been observed by the authors in a patient in whom the infection was controlled by penicillin therapy, but who was left, nevertheless, with a completely incompetent valvular orifice and who subsequently died of cardiac failure. Other investigators have mentioned similar experiences. Frequently, indications of altered valvular structure may be found in the changing cardiac murmurs heard during therapy. Following successful therapy, the scar tissue in the healed vegetations may contract, or adjacent valve cusps may become agglutinated, thereby increasing the valvular insufficiency and inducing heart failure. Occasionally, changes in the electrocardiogram may be noted, as a consequence of heart muscle damage and repair. Hence, allowance must be made for a reduced cardiac reserve in the after-care of patients that recover from the disease.

Splenomegaly, present in the majority of cases of subacute bacterial endocarditis, has been observed to diminish successfully after penicillin treatment has been started. Occasionally, a spleen which is only slightly enlarged may regress completely during the course of the therapy. There have been no reports of splenic enlargement once treatment was started. Although the anatomic explanation for regression of splenomegaly is not known, it may be associated with the reduction of inflammatory cells which are known to predominate in the spleen in bacterial endocarditis.

Renal involvement, i e , embolic glomerulonephritis, may be suspected in the presence of such urinary findings as albumin, leukocytes, red blood cells, and granular and hyaline casts The formed elements in the urine as well as the albuminuria tend to disappear during the course of treatment. Bloomfield, Armstrong, and Kirby (33) noted residual evidence of embolic glomerulonephritis in about 50 per cent of the patients that improved after treatment Longer periods of observation after recovery are required before conclusive statements can be made as to the fate of the renal lesions. Renal infarction, which is commonly encountered in the presence of embolic manifestations, is not a significant complication. Healing may occur rapidly, as shown by the necropsy findings in patients who died of heart failure after effective control of the disease

Clubbing of the fingers, which is estimated to occur in about 30 per cent of patients with subacute bacterial endocarditis, has been seen to regress following penicillin therapy. This has also been the authors' experience

Agents, of the Office of Scientific Research and Development, are still in progress and have not yet been reported.

Ten months after the first report by Loewe *et al.* (23) of 7 successfully treated cases, Loewe (25) recorded a much larger group in which the original 7 were included. Of the 54 patients treated 16 died, a recovery rate of about 70 per cent. However, only 13 were considered to be treatment failures, 3 having died of cardiac failure after control of the disease. This would raise the incidence of recovery to 76 per cent. The second large series of cases reported was that of Dawson and Hunter (24). They treated 20 patients, and recorded 15 recoveries, 3 fatalities, and 2 relapses; the incidence of reported recoveries is 75 per cent, a figure nearly identical with that reported by Loewe. In an addendum to their report, these authors added 7 patients with termination of the infection in 6 and relapse in the seventh. Out of another series of 29 cases (32) the recovery of 19 was recorded, with 6 fatalities, 2 of which were considered instances of controlled infection with death due to cardiac failure, and 4 still under treatment at the time of the report. If we exclude these, the incidence of recovery is 76 per cent. Bloomfield, Armstrong, and Kirby (33) treated 11 patients with apparent recovery in 10; of these 1 died subsequently in cardiac failure and 1 patient died on the fourth day of treatment. Meads, Harris, and Finland (26) obtained successful results in 7 of 10 patients with recurrence of the infection in 2 and fatality in 1. They reported severe heart failure due to extensive damage to the cardiac structures in the fatal case.

The striking similarity in the rates of reported recoveries is not accidental, but an accurate statistical evaluation of the percentages of recovered cases must await further reports. Since these investigations are fairly representative of various samplings, it is safe to assume that with adequate treatment the anticipated results of successful treatment of subacute bacterial endocarditis may be from 70 to 75 per cent. A long follow-up, with the exclusion of relapsing cases or fatalities in which postmortem examination may demonstrate continuation of the disease process on the valves, is necessary before a more exact estimate of complete recovery after penicillin therapy is possible.

An analysis of the fatalities after control of the infection almost uniformly indicates the predominance of cardiac failure. The danger of this complication has been amply discussed. It will undoubtedly always remain a problem, although in time the incidence may be reduced by careful attention to early and intensive treatment.

The duration of remission of the disease, as reported to date, varies from

improved methods of manufacture has failed to eliminate this complication completely, particularly when high concentrations of the drug are used. Thrombophlebitis is in part induced by trauma to the wall of the vein due to the alkalinity of penicillin sodium solutions Changing the position of the needle daily may reduce the incidence of thrombophlebitis to a minimum. Nevertheless, this complication may be anticipated when therapy is continued for many weeks, and occasionally intramuscular injections must be substituted or alternated in order to permit resolution of the angiitis. It has been claimed that heparinization reduces the incidence of thrombophlebitis (25), thereby facilitating the continuation of intravenous therapy. However, often thrombophlebitis supervenes rapidly following the discontinuation of heparin, and it occurs not uncommonly during therapy, even though the blood coagulation time is prolonged to 30 or 60 minutes.

The only significant complication of the intermittent intramuscular injection of penicillin is pain at the site of injection. It is well known that tolerance to pain is a variable factor and frequently cannot be used as a guide to the irritating qualities of the solution Many patients will tolerate intramuscular injections every hour or two for periods of 4 to 6 weeks without complaint, whereas others will object strenuously to as little as 4 daily intramuscular injections. It has been found that the sodium salt of penicillin is the least irritating. The calcium salt can likewise be used for parenteral therapy with impunity Penicillin X and G have recently been introduced with the claim that higher and more prolonged blood levels are obtained. In a limited study with penicillin X the authors noted the more frequent complaint of pain at the site of intramuscular injection by patients who had tolerated ordinary penicillin very well

Results Reported to Date

Although there is marked variation in the type of cases of bacterial endocarditis treated by different investigators, certain common therapeutic experiences were noted Some patients responded promptly and remained symptom-free almost from the very inception of penicillin therapy Others succumbed before adequate penicillin therapy could be administered Still others required from 1 to 5 courses of treatment before success or failure was established Nonetheless, the incidence of recoveries reported by different investigators shows remarkably little variation.

The reported recoveries vary from descriptions of single cases to fairly large series A summary of these cases is not possible at present since many studies, established by the Committee on Chemotherapeutics and Other

viridans and found that the infection persists on the valve not only because the deposit of fibrin exceeds the invasion of white blood cells and fibroblasts, but because the fibrin offers an excellent medium for growth They felt that the fate of the infected focus in the experimental animals was determined by the balance of fibrin deposited and of granulation tissue ingrowth, and emphasized the sluggish inflammatory reaction of the valve as being responsible for the early development of the infection.

Kelson and White (6) in 1939 first introduced the combined use of heparin and sulfonamides by continuous 24 hour intravenous drip for a period of about 14 days, which elevated the clotting time of the blood to about 1 hour. Seven patients with subacute bacterial endocarditis were treated by them initially. However, the adjuvant use of heparin contributed little ultimately to the number of apparent recoveries. In a complete report on their treatment of subacute bacterial endocarditis by sulfonamides, with and without anticoagulants, White, Matthews, and Evans (12) showed only 5 apparent recoveries in a group of 88 cases, an incidence of 5 7 per cent, whereas Lichtman (4) was able to collect 489 cases from the literature treated by sulfonamides alone with a reported incidence of apparent recoveries of 4 per cent.

McLean, Meyer, and Griffith (68) studied 67 patients with bacterial endocarditis treated with heparin and sulfonamides, and came to the conclusion that the results obtained did not warrant any further trial of treatment with heparin according to the plans used by most investigators. The complication of hemorrhage in various organs, with occasional fatalities directly attributable to heparin, was felt by them to be too frequent and too serious to permit the use of the drug as a routine adjuvant It might be mentioned also that these authors objected to the use of continuous intravenous infusion for periods of 2 or more weeks since the heart was already damaged by bacterial endocarditis and cardiac failure might supervene Katz and Elek (69) recommended the abandonment of heparin therapy in subacute bacterial endocarditis after their experience with a number of cases, as well as a review of the reports in the literature, finding that the disadvantages far outweighed the advantages.

While the value of anticoagulants in combination with sulfonamide therapy was undergoing critical analysis, Loewe and his co-workers (23) reported on the first group of cases of bacterial endocarditis successfully treated with penicillin and heparin. The previous failures reported by Keefer and his associates (22) stood in such sharp contrast to this successfully treated series that subsequent investigators appear to have been more influenced by the concept that heparin was possibly the important

3 months to 2 years. The first group of successfully treated patients (23) probably represents the longest remission. Subsequent series include cases in which the duration of recovery is necessarily somewhat shorter. It is commonly said that a long period of observation may be necessary before adequate conclusions as to the effectiveness of penicillin therapy can be drawn and, conservatively, one may quite agree with this statement. However, when one considers the fact that subacute bacterial endocarditis was almost uniformly fatal, the present incidence of 76 per cent of apparent recovery for periods ranging from 3 months to 2 years represents a significant achievement and warrants much optimism

Relapse after treatment is variable, occurring either immediately or many months after cessation of therapy. The immediate relapses differ somewhat from those in which the relapse follows apparent control of the infection. In the former, it is apparent that the bacteremia has been controlled, but as soon as penicillin is no longer present in the blood stream the unaffected valvular lesion again begins to feed organisms into the circulation. A second or third course of therapy, immediately instituted, may often suffice to bring about healing of the primary focus on the valve. The conditions which obtain in late recurrences will be discussed further on. It is safe to assume that most instances of early recurrence are due either to inadequate penicillin dosage or to insufficient duration of therapy. Hence, the successes obtained following second, third, or more courses represent corrections of this deficiency. Such recurrences were commonly encountered in the early stages of penicillin therapy when the supply of the drug was limited and when dosage schedules were modest In most instances, the introduction of large doses has reduced the number of early recurrences. It may be expected that in the future the use of fairly large doses over long periods of time will eliminate such complications.

Use of Anticoagulants

The disappointing results of sulfonamide therapy in the treatment of subacute bacterial endocarditis led to a search for certain adjuvant means that might enhance the effect of the drug It was felt that a greater penetration of the drug into the focus on the heart valve would facilitate sterilization and consequent healing. Since anatomic studies of the vegetations in subacute bacterial endocarditis had demonstrated the presence of surface fibrin deposits, it was postulated that a diminished coagulability of the blood would reduce the fibrinous barrier to the penetration of sulfonamides The experiments of Freedman *et al* (67) gave support to this concept. They produced experimental bacterial endocarditis with Streptococcus

ficial influence upon the incidence of thrombophlebitis, the untoward reactions that occur in some instances necessitate careful consideration of the need for the drug. Furthermore, as has been mentioned, other contraindications to the use of intravenous therapy, namely, its unwieldiness as well as the risk of using large quantities of fluid in patients with hearts already damaged, do not justify the routine use of a continuous intravenous method even if the incidence of thrombophlebitis is diminished by heparin. The current effective results obtained by means of intramuscular injections spaced at 3 hour intervals, as well as the other advantages of this method (see page 317), appreciably reduce the need for continuous intravenous therapy. It may be anticipated that the influence of the concept prevailing during the treatment of bacterial endocarditis with sulfonamides will gradually disappear as numerous experiences further demonstrate that continuous intravenous penicillin therapy or, preferably, intermittent intramuscular injection of penicillin is effective without the questionable adjuvant effect of heparin or other anticoagulants.

Treatment of Bacteria-Free Cases

Libman (2) introduced the term "bacteria-free stage" of subacute bacterial endocarditis in 1910 in order to separate a special group of patients, in whom an advanced degree of healing of the valve lesions had occurred, from those with active endocardial disease in which the blood cultures were found to be sterile. He noted that patients in the bacteria-free stage of the disease, in contrast to those with active involvement of the heart, died of sequelae such as cardiac failure, renal insufficiency due to subacute or chronic glomerulonephritis, progressive anemia, and occasionally embolic *accidents, rather than from the primary disease itself. The postmortem* examination of the heart in the bacteria-free cases frequently demonstrated that stained smears and tissue sections of the vegetation were free from the bacteria, occasionally, a few organisms could be found on careful search. In addition, the vegetations often showed advanced organization, fibrosis, and at times even calcification. The clinical course of the bacteria-free stage was characterized by the presence of pronounced secondary anemia, marked splenic enlargement, and the striking brown pigmentation of the face and the back of the hands, commonly referred to as the café-au-lait color. Petechiae, Osler nodes, and other striking embolic manifestations of the active stage, as well as diffuse joint pains, were absent.

An accurate clinical distinction between active cases of subacute bacterial endocarditis in which negative blood cultures are reported and the bacteria-free stage of the disease may not always be possible. With good tech-

factor rather than the method of administration and dosage of penicillin used Thus, Dawson and Hunter (24) reported a series of 20 cases of bacterial endocarditis in which heparin was used in 15. Their first series of 5 cases, which represented a pilot experiment, was treated without heparin. Of these 2 patients recovered; one relapsed and was subsequently treated by Loewe with penicillin and heparin; a third died; and the fourth patient had to be retreated. Thus, the subsequent 15 cases were given heparin by intravenous drip or by the subcutaneous method as devised by Loewe and Rosenblatt (70) to obviate the difficulty of continuous intravenous infusion. Dawson and Hunter (24), however, in an addendum to their report added 7 cases, 5 of which were treated without heparin, and concluded that the response was as favorable in this group as in those cases in which heparin was used. Bloomfield, Armstrong, and Kirby (33) treated a group of 11 patients with penicillin alone and reported 8 recoveries Meads, Harris, and Finland (26) treated 9 cases, some with heparin, and found no advantage to justify the additional efforts and risks of heparin Gerber, Shwartzman, and Baehr (32) used heparin in the first 4 cases treated and then resorted to penicillin alone in the subsequent 25 cases, with 19 recoveries, a remission rate comparable to that reported by other investigators who employed heparin.

A summary of the various experiences of many investigators in the treatment of bacterial endocarditis with penicillin reveals no advantage from the use of heparin Katz and Elek (69) point out that heparin was originally combined with sulfonamide therapy in the hope that the chemotherapeutic agent would penetrate into the vegetation and check the continued growth of the infecting organism, thereby accelerating healing of the valve However, this healing has not been demonstrated on postmortem examination. Leach and his co-workers (71) state that the postmortem examination in several cases revealed little effect upon the vegetation, either from chemotherapy (sulfonamides) or heparin The contention by Kelson (72) that an unusual degree of healing occurs with heparin therapy has not been confirmed by other investigators. While it would be highly desirable to facilitate the penetration of a chemotherapeutic agent into the ulcerated lesion on the valve, it has not been demonstrated that heparin or any other anticoagulant serves that purpose

It was later stated that heparin might be of value in reducing the incidence of thrombophlebitis at the site of intravenous therapy. The amount of heparin normally employed is calculated to increase the coagulation time from 30 to 60 minutes An increase above that is recognized to be dangerous. While it is possible that such a moderate increase may exert a bene-

ficial influence upon the incidence of thrombophlebitis, the untoward reactions that occur in some instances necessitate careful consideration of the need for the drug. Furthermore, as has been mentioned, other contraindications to the use of intravenous therapy, namely, its unwieldiness as well as the risk of using large quantities of fluid in patients with hearts already damaged, do not justify the routine use of a continuous intravenous method even if the incidence of thrombophlebitis is diminished by heparin. The current effective results obtained by means of intramuscular injections spaced at 3 hour intervals, as well as the other advantages of this method (see page 317), appreciably reduce the need for continuous intravenous therapy. It may be anticipated that the influence of the concept prevailing during the treatment of bacterial endocarditis with sulfonamides will gradually disappear as numerous experiences further demonstrate that continuous intravenous penicillin therapy or, preferably, intermittent intramuscular injection of penicillin is effective without the questionable adjuvant effect of heparin or other anticoagulants.

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nic, many active cases may yield the infecting organism on repeated attempts, though negative blood cultures were obtained at the outset. Furthermore, at some time in the course of the bacteria-free stage, the responsible organism may still be present on the heart valves. It is advisable, therefore, to include both groups of cases in a discussion of the treatment of bacterial endocarditis in which the blood cultures are negative. It was found (5) at autopsy that 19 of 51 cases that had spontaneously become bacteria-free died of a complicating diffuse glomerulonephritis and renal insufficiency, and that this complication rarely occurred in cases with continued bacteremia. The presence of a true glomerulonephritis is therefore a means of differential diagnosis. It is interesting to note that glomerulonephritis has not been reported when recovery has followed penicillin therapy.

Inasmuch as between 90 and 95 per cent of all cases of subacute bacterial endocarditis are caused by gram-positive cocci (such as Str. viridans, Str. faecalis, Str. haemolyticus beta), the indifferent or nonhemolytic streptococcus, or Staph. albus—all organisms which are known to be sensitive in varying degrees to the antibiotic effect of penicillin—a therapeutic trial should be made in every instance.

Cases of clinically unquestionable subacute bacterial endocarditis occur in which numerous blood cultures are negative, but which often show at postmortem examination an extensive, ulcerative valvular lesion from which bacteria may be recovered at times The anatomic alterations are indicative of a severe infection, emphasizing the need for intensive therapy. In the absence of a positive blood culture, however, there are no criteria as to the penicillin sensitivity of the infecting organisms and the dosage and duration of treatment cannot be established It would therefore be advisable to administer large doses of penicillin over a period of 4 to 8 weeks in order to cover the possibility that the underlying infection was caused by an organism of moderate penicillin resistance. The authors recommend a minimal intramuscular dose of 100,000 units every 3 hours for a period of 4 to 8 weeks, as in the treatment of the active stage of the disease in which the blood cultures are positive.

In the absence of positive blood cultures, the only criterion by which adequate dosage can be established is the clinical response of the patient, as judged by the course of the temperature, the diminution in the erythrocyte sedimentation rate, the reduction of the white cell count, and the rise in hemoglobin. An additional valuable index of the effectiveness of penicillin therapy in these cases is the diminution and gradual disappearance of embolic phenomena. When the case is considered to be typical of the

bacteria-free group described by Libman (2), special consideration must be given to penicillin dosage. In these instances, there is advanced healing of the valvular lesion and what few bacteria remain are usually found deeply embedded in the organizing vegetation. In order to assure sterilization of such lesions, rather large doses of penicillin must be employed. The high peak of penicillin blood level which is obtained with large single intramuscular doses may facilitate the penetration of the drug into the dense avascular areas. Hence, the use of 200,000 or 300,000 units every 3 hours intramuscularly is warranted in these cases. Although the complications of the bacteria-free stage, for example, renal insufficiency, may be so far advanced that the chance of ultimate recovery is reduced appreciably, a therapeutic trial of penicillin is worth while.

Several investigators have reported on the treatment of patients with subacute bacterial endocarditis with negative blood cultures. The authors, too, have accepted for treatment several such patients, with apparently successful results. There has been no report of the treatment of a classical case in the so-called bacteria-free stage, and a long time may elapse before final judgment can be passed upon the value of penicillin in this stage. However, the total lack of toxicity and great availability of the drug offer a means, for the first time, of treating this small group of cases, hitherto refractory to any form of therapy.

Signs and Symptoms after Cessation of Therapy

A common difficulty encountered in the evaluation of adequate therapy is the presence of various signs after penicillin has been stopped Occasional patients whose course clearly indicates that the infection had been controlled not infrequently present signs, shortly after treatment, which strongly suggest a continuation of the disease process or a relapse. This experience has at times given rise to a pessimistic evaluation as to the value of penicillin therapy in a given case. However, it is important to recognize that certain signs may occur in the post-therapeutic recovery phase without indicating either failure of response or relapse.

Fever, leukocytosis, embolic phenomena, and accelerated sedimentation rate may persist singly or in combination after the completion of treatment. Observation of the temperature during convalescence may show an occasional rise to 100 F. to 102 F. which is transient in character and for which there may be no explanation Other patients continue to show low grade fever, rarely exceeding 100 F., for some weeks after cessation of therapy. Further, occasional patients will report a more or less persistent subfebrile course for many months after discharge from the hospital as apparently

cured One can only speculate as to the cause of this low grade fever. In the absence of demonstrable persistence of the infection or of rheumatic reactivation, we are at a loss to explain this finding. Necrosis of an old infarction may play a role in some instances. Only a long follow-up of the ultimate fate of recovered cases offers any hope for the solution of this problem.

Not uncommonly a slight to moderate elevation of the sedimentation rate and a mild leukocytosis may be noted for a number of weeks after treatment has been stopped. As a rule, these laboratory evidences of active infection, assuming the absence of other causes, usually return to normal limits within 2 months after cessation of therapy. The presence of either finding at later periods requires further investigation in order to rule out the possibility of a relapse.

The most disquieting sign noted occasionally after treatment is the occurrence of embolic phenomena. While in no way comparable in degree and extent to that seen during the active stage of the disease, nevertheless the appearance of this symptom is often cause for alarm. However, the accumulated observations of many investigators who carefully followed penicillin-treated cases of bacterial endocarditis over a period of many months indicate the relative benignity of this sign. Anderson and Keefer (34) described the appearance of a mycotic aneurysm of the right common iliac artery 75 days after treatment was completed in a patient who ultimately completely recovered from the disease In most instances, embolic phenomena after therapy are less significant than the one just mentioned Since the experience with the penicillin treatment of subacute bacterial endocarditis is, on the whole, still rather limited, the appearance of embolic manifestations after therapy is discontinued, warrants the suspicion of a relapse, and calls for careful study

Recurrences

A relapse may occur at any time after treatment has been completed For the present, it is important that a distinction be made between early and late recurrence of the disease. In the first experiences with penicillin treatment of bacterial endocarditis, early recurrences were observed fairly frequently. As the need for larger doses of the drug and longer periods of treatment became evident and the resistance of the infecting organism was correctly evaluated, the incidence of early relapse diminished appreciably. Multiple courses of therapy in rapid succession became less common, and control of the disease was effected in a shorter period of time, so that the

sequelae which characterized the uncontrolled course of bacterial endocarditis were reduced to a minimum.

In the days of sulfonamide therapy, it was frequently observed that bacteria developed fastness to the sulfonamide drugs. Similar experiences were anticipated when penicillin was introduced, and it was soon demonstrated *in vitro* that penicillin fastness could be acquired by bacteria exposed to gradually increasing doses of the drug (73). Occasional instances of clinically acquired penicillin fastness appeared in the literature. Gallardo (74) found that 9.4 per cent of 85 strains of pathogenic staphylococci recovered from human wound infections acquired an increased resistance in the course of penicillin therapy. He believed that the penicillin-fast organisms were derived from parent strains previously sensitive and estimated that it required from 5 to 40 days for this fastness to develop. Acquired penicillin resistance of the viridans streptococcus in subacute bacterial endocarditis, however, appears to be relatively uncommon. Florey and Florey (21), who reported the first attempt at penicillin therapy of bacterial endocarditis, noted that the causative organism, Str. viridans, showed an increased resistance toward the end of therapy. Loewe (25) reported one instance in which the organism developed a fortyfold increase in resistance to penicillin during therapy Many investigators (26,33,34) have observed recurrences of the disease with no increase in penicillin resistance of the causative organism. In fact, it was noted that in one instance the bacteria showed less penicillin resistance than when isolated prior to the first course of penicillin therapy. The authors had a similar experience Whatever the cause of acquired penicillin resistance may be, it appears that it is an uncommon occurrence in bacterial endocarditis Relapses, therefore, are generally not attributable to penicillin resistance acquired during therapy.

A late recurrence may be considered one in which the signs and symptoms of the disease appear from 3 to 8 months after completion of treatment. There is no adequate explanation to account for these cases It is possible that as the valve heals bacteria may be covered up by granulation tissue and that they remain viable for a long period of time in this walled-off area The suggestion has been made that instances of late recurrence may actually represent a newly acquired infection after recovery Neither concept is subject to proof at the present time, but it seems safe to assume that a late recurrence may be one in which complete healing has failed to occur. Hence, in the re-treatment of such cases special attention must be paid to adequate dosage over a long period of time, and, as discussed previously, the repeated intramuscular injection of large doses every 3 hours may facilitate penetration of the drug into the relatively avascular valve It is

therefore recommended that doses as large as feasible be used in treating a case showing late recurrence of the disease.

Adjuvant Therapy

Prime consideration must be given to the proper administration of penicillin in the treatment of bacterial endocarditis. However as in other severe infections the usual supportive measures must not be overlooked. These include the treatment of anemia with transfusions, adequate diet, and vitamin therapy when indicated, and the correct management of cardiac complications. Fortunately, as there is no incompatibility between penicillin and any other drug, salicylates may be employed unhesitatingly when occasionally there is co-existence of rheumatic activity.

The nontoxic qualities of penicillin have led some investigators to overlook completely the possible value of the sulfonamide drugs as adjuvant to penicillin A synergistic effect of sulfonamide and penicillin has been demonstrated *in vitro*. A number of investigators employed sulfonamide drugs with penicillin early in the treatment of bacterial endocarditis primarily because the clinical response to penicillin alone did not appear to be satisfactory, a feature which was subsequently corrected when larger doses of the latter were used Thereafter, sulfonamide therapy was reserved for those cases in which the failure of therapy appeared evident despite adequate penicillin doses At the present time the same investigators would recognize that what was considered adequate dosage then was perhaps insufficient. Numerous studies of the sensitivity of the vast majority of organisms isolated from cases of subacute bacterial endocarditis indicate a much greater sensitivity to penicillin than to sulfonamides However, an occasional case may be encountered in which the reverse may be true, and in such cases it would be advisable to combine both penicillin and sulfonamides in the hope that control of the infection might result. Aside from such instances, there is an additional value in the prophylactic use of both drugs in subacute bacterial endocarditis, as discussed below.

Surgical Procedures Including Dental Extraction

Occasionally surgical intervention may become necessary in the presence of an active subacute bacterial endocarditis Past experience has demonstrated that surgical procedures may be employed without fear of unusual complications, and since the introduction of penicillin there is even less reason to avoid essential operations. Although the causative organism

rarely gives rise to suppuration, it is still advisable to ensure sterilization of the blood stream before surgical intervention.

Of greater importance, however, is the use of penicillin in patients with rheumatic cardiovalvular disease and in arrested cases of bacterial endocarditis. It is well known that transient bacteremia may follow surgical procedures, parturition, or various diagnostic methods, such as cystoscopy. In fact, the last-mentioned is occasionally responsible for the precipitation of an acute or subacute bacterial endocarditis by Enterococcus, an organism not uncommonly found in the urinary tract. Penicillin should be injected immediately prior to surgical procedures and continued for a period of 12 to 24 hours thereafter An attempt should be made to maintain high blood levels of penicillin following cystoscopy, since organisms such as Enterococcus, which invade the blood stream following this procedure, are known to be especially penicillin resistant.

One of the most common surgical procedures known to be responsible for the onset of bacterial endocarditis is the extraction of teeth It has been estimated that approximately 25 per cent of all cases of subacute bacterial endocarditis follow dental procedures In the recent past it was customary to administer sulfonamides before and for 48 hours after dental extraction This prophylactic therapy may often have been ineffective, for many strains of the viridans streptococcus liberated into the blood stream during the removal of teeth are known to be resistant to sulfonamides. Nevertheless, the practice was to be highly recommended, and it is equally important that a similar routine be followed with penicillin, both in patients with rheumatic heart disease and in persons who have recovered from subacute bacterial endocarditis Again, since the resistance of the organism which may enter the blood stream after dental extractions cannot be known, it would be advisable to use large single doses intramuscularly, such as 100,000 or 200,000 units every 3 hours, in order to ensure inhibition of the invading bacteria. Loewe advocates the removal of all infected teeth under continuous penicillin therapy in all patients who have recovered from subacute bacterial endocarditis through the use of this antibiotic

There is no contraindication to the simultaneous use of sulfonamides to control the transient bacteremia Chemotherapy with sulfonamides and penicillin may not only have an influence on the transient bacteremia but may also inhibit the postoperative proliferation of bacteria at the site of injury and reduce the likelihood of secondary invasion of the blood stream. What has been said with regard to dental extraction holds as well for other minor surgical procedures, such as tonsillectomy or sinus operations, in patients with rheumatic heart disease.

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Treatment of Cases Infected with Organisms Highly Resistant to Penicillin

It appears that the majority of cases of bacterial endocarditis are infected with strains of bacteria moderately resistant to penicillin, but occasionally a highly resistant organism is cultured from the blood stream and presents a difficult problem in therapy. It has been previously mentioned that intermittent intravenous therapy, by introducing the penicillin solution every 3 hours into the flask of a continuous intravenous infusion of normal saline, may help solve this problem through the very high blood levels that follow. However, such levels are of even shorter duration than those which obtain after intramuscular injection. Although such intermittent therapy may be effective, it would be more reassuring if these extremely high blood levels could be maintained over longer periods of time The simultaneous intravenous instillation of *p*-aminohippuric acid may solve this difficulty by blocking the rapid renal excretion of the drug, as shown by Beyer *et al* (55) Studies of this type with massive doses of penicillin have not yet been reported. In view of the severity of the disease, the use of benzoic acid by mouth to achieve the same result might be indicated, despite the gastric irritation likely to be induced when this drug is used over long periods of time

Determination of Dosage and Duration of Therapy

The authors have expressed the opinion that a minimum treatment period of 4 weeks, with an optimum of 8 weeks, be established in order to achieve maximum therapeutic benefits in the treatment of subacute bacterial endocarditis The schedule of dosage recommended was 100,000 to 200,000 units of penicillin to be given intramuscularly every 3 hours Undoubtedly in some cases this may represent excessive dosage with some waste of drug In other instances, even larger amounts may have to be used, depending upon the resistance of the causative organism. It has also been mentioned that there are no fixed criteria by which dosage and duration of therapy can be determined. Whether or not such criteria may be established in the future cannot be predicted The difficulties that lie in the way are the unknown factors of the degree of valvular involvement, the penetrability of penicillin into the lesion, and the rapidity and extent of valvular healing Despite the lack of information with regard to these factors, it would be advisable to persist in the treatment of a resistant case even though failure may seem to be a foregone conclusion The drug is nontoxic and at present relatively inexpensive Since there are no other means for approaching this disease, multiple courses of therapy with mas-

Prognosis

Very little can be said with respect to the prognosis of patients with subacute bacterial endocarditis that have responded to penicillin therapy, since the longest periods of observation do not yet exceed 2 years The vast majority of recovered cases are currently of less than 15 months' duration An analysis of the reported recoveries indicates that approximately 65 per cent of these patients are able to function in a manner comparable to that prior to the onset of the disease Obviously, the resumption of functional capacity must vary with the degree of resultant cardiac damage, but other than this there are no sequelae of clinical significance

The prognosis in apparently recovered cases should be guarded for the first 3 months, since most recurrences occur within this period. When the patient has remained well for a year, it may safely be assumed that recovery from the infection has occurred However, the possibility of a reinfection must always be borne in mind Possibly, as is the case with healed syphilis, multiple attacks of the disease may be expected in future years

Problems to Be Solved

Maintenance of a Continuous Supply of Penicillin in the Blood

It has been pointed out that the desideratum of penicillin therapy is the presence of a very high level of the drug in the body fluids. This has not been achieved to date because of the complications that follow the intravenous introduction of concentrated solutions of penicillin by the continuous drip methods. Intramuscular therapy, although preferrable in most instances, presents the disadvantage that high blood levels persist only for short periods, due to the rapid excretion of the drug Neither deficiency has been overcome by oral administration, since enormous quantities of drug must be given at frequent intervals in order to achieve continuous high blood levels. Occasionally, it may be desirable to resort to oral therapy when short periods of treatment are indicated. Benzoic acid by mouth is the most promising of the various methods introduced to achieve higher blood levels over long periods of time by interfering with the rapid renal excretion of the drug. Unfortunately, the gastric symptoms which often follow the ingestion of benzoic acid do not permit its prolonged use and its value as an adjuvant therapeutic measure in the treatment of subacute bacterial endocarditis is therefore limited Some means will have to be found to overcome the difficulty of maintaining a constant high penicillin blood level, in order to reduce therapeutic failures, particularly in infections caused by bacteria of high resistance

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sive doses must be tried to the very end. The reasonableness of this attitude was born out recently in the treatment of a patient with persistently positive blood cultures, *even though* the infecting organism was susceptible to penicillin in low concentrations. The dose was *increased with each* course of therapy until the patient was receiving 200,000 *units every* 2 hours, at the end of 5 weeks of this dosage, control of the infection was *obtained*, a total of 127,000,000 units of penicillin having been used in the course of 3 months of almost continuous treatment.

Summary

It has been amply demonstrated that penicillin is an effective agent for the treatment of subacute bacterial endocarditis. The ease of administration and the relative nontoxicity of penicillin, however, should not beguile one into uncontrolled treatment of the disease. Failures may follow unless the dosage is adequate and the duration of treatment sufficiently long to allow complete healing of the valvular lesions. The determination of the penicillin sensitivity of the causative organism and frequent estimations of the penicillin blood level during therapy are important guides to proper dosage. Although the clinical response is prompt and satisfactory in most cases, the subsidence of symptoms cannot be relied upon as evidence of effective therapy. Prompt recurrence of all symptoms has been observed in instances of insufficient dosage or duration of treatment when penicillin is withdrawn. The same holds for negative blood cultures during penicillin administration. On the other hand, if the blood cultures remain sterile, the occasional appearance after penicillin is stopped of such symptoms as low grade fever, embolic manifestations, or slight elevation of the erythrocyte sedimentation rate, does not warrant the conclusion that a relapse has occurred The patient must be observed closely. Often these symptoms will be seen to subside, a persistence of the symptoms, however, should arouse the suspicion of a recurrence of the disease despite the presence of negative blood cultures.

Intensive treatment of all cases is indicated as soon as the diagnosis is made and the penicillin sensitivity of the infecting organism is established Thereby, valvular destruction will be reduced to a minimum and the chronic invalidism resulting from prolonged, inadequate therapy will be obviated. Consideration must be given at all times to the fact that myocardial damage may be present during the course of the disease This is especially important in an evaluation of the functional capacity of the patient after recovery is achieved

At present, the most desirable route and method of administration of

penicillin for the treatment of subacute bacterial endocarditis is the intermittent intramuscular injection, preferably every 3 hours. Therapy should be continued for a period of 4 to 8 weeks. The use of continuous intravenous infusions of penicillin is frequently attended by thrombophlebitis which often interdicts the employment of this method. Except in occasional instances of very high penicillin resistance of the infecting organism, it offers no advantages over intermittent intramuscular therapy. The oral administration of penicillin has so far proved impracticable because of the very large quantities of drug which have to be taken in order to achieve the desired blood levels This method may be of value in the prophylaxis of the disease during minor surgical procedures, especially the extraction of teeth.

To date, the longest period of remission of patients recovered from bacterial endocarditis is about 2 years. An incidence of remission of between 70 and 75 per cent may be anticipated when adequate therapy is instituted The ultimate fate of recovered patients remains to be determined However, the result is most encouraging when one compares it with an incidence of 1 per cent of spontaneous recovery and of 5 per cent after sulfonamide therapy The possibility of a late recurrence or re-infection may always be present, but with careful attention to the essentials of proper therapy, these complications can be reduced to a minimum. It is also likely that the incidence of remissions may in the future be increased above the remarkable rate already achieved

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Use of Penicillin in Infections Other Than Bacterial Endocarditis

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Introduction

In 1928 the modest bacteriologist in the Inoculation Department of St. Mary's Hospital in London examined the clear zone around the contaminating mold colony on his agar plate which had previously been completely covered with staphylococcus colonies. He immediately set out to look for the diffusible substance produced by the mold which might have been responsible for the lysis of the organisms and which prevented the growth of the staphylococci. The mold was found to be a species of Penicillium, and Fleming gave the name penicillin to the diffusible substance which it produced in the culture tube and on agar plates.

Following the publication of the first papers by the discoverer the literature on penicillin remained notably barren until after the appearance of the historic reports by the Oxford group of workers in 1940 and 1941. This was partly the result of limited facilities for making adequate amounts of preparations of penicillin for general clinical use, except perhaps for topical applications Adequate amounts became available only after large-scale production began, which was stimulated following Florey's visit to this country in the summer of 1941 Until that time penicillin was used to a minor extent as a bacteriologic aid in the isolation of hemophilic and other gram-negative bacteria It is still used somewhat for that purpose and for the elimination of susceptible organisms during virus isolations, but such uses have been completely overshadowed by its widespread clinical applications

Production of Penicillin

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tially of inorganic salts and glucose After inoculation of the medium with spores of the mold and incubation for 6 or 7 days, a "mold mat" covers the

surface of the broth and the yellow drops of penicillin-containing liquid appear on the surface of the mat and diffuse into the medium This method of surface culture involves the use of thousands of flasks or bottles, each containing at most several liters of the medium, inoculated and incubated in suitably designed rooms, in order to obtain a single batch of crude liquor from which the penicillin could be extracted.

More productive strains of Penicillium were discovered Proper media, improved particularly by the addition of corn-steep liquor, and by more precise conditions for penicillin production, were developed. The so-called "deep tank" or "submerged" method of penicillin production involves units, each thousands of gallons in capacity, compared to the few liters capacity of the flasks used in the surface methods.

Irrespective of the method of production, the crude penicillin must be purified by extraction with various solvents such as acetone, amyl acetate, or chloroform. Adsorbing agents are often employed as one step in this process. Most of these processes must be carried out at reduced temperatures The final extraction involves conversion of the free penicillin into a salt—usually the sodium or calcium salt The penicillin originally produced by the Oxford workers contained about 40 to 50 units per milligram Commercial sodium penicillin or calcium penicillin has a potency of not less than 500 units per milligram Many batches of the commercial products assay as high as 1,100 to 1,200 units per milligram, or about 80 per cent pure penicillin Recently there became available a commercial product which assayed better than 1,600 units per milligram—almost pure penicillin

Mutant strains of Penicillium may apparently develop in the course of growth and production. At least four separate, distinct forms of penicillin have been described and can be obtained from cultures made with the same strain. Differences in the activity of these distinct forms of penicillin have been revealed Recent observations on the action of penicillin on Treponema pallidum suggest that, in addition, considerable activity may actually reside in parts of the penicillin solution which have hitherto been discarded in the process of purification.

Physical and Chemical Properties of Penicillin

As finally prepared for parenteral use, penicillin is a dry powder ranging in color from light yellow to dark brown The commercial lots now released for sale must contain at least 500 units per milligram and not more than 2 5 per cent moisture Most of them are of higher potency and contain only about 1 per cent moisture or less. The material represents a mixture of sodium salts of organic acids, of which more than one-third is sodium peni-

cillin. The products are rigorously tested for potency, sterility, toxicity, and pyrogens under the control of the Food and Drug Administration.

The empiric formula originally proposed by the Oxford workers for the barium salt was $C_{24}H_{32}O_{10}N_2Ba$ or $C_{23}H_{30}O_{10}N_2Ba$. The analysis of the material prepared by Meyer and his associates best fitted the formula $C_{14}H_{19}NO_6$ or $C_{14}N_{17}NO_5 + H_2O$ Exact details concerning the later developments in the chemistry of penicillin were withheld from publication until December, 1945. At that time it was revealed that the common forms of penicillin all have the empiric formula $C_9H_{11}O_4SN_2R$, the structure of R varying in the different forms (see page 355).

Penicillin is a strong organic acid. It is inactivated at very low or high *p*H but is moderately stable between *p*H 6 and 7. It is highly soluble in water and alcohol but is inactivated by the latter. Pure crystalline penicillin, which is now available for routine treatment, is colorless or white; the yellow or brown-to-orange color of the commercial products probably depends on their impurities and on the nature of their contaminants

The more recent preparations are stable. As a powder, some preparations retain full potency for at least 60 days No significant loss in potency occurred in tests on commercial samples stored at 8 C during the course of a year, at ordinary room temperature (about 25 C.) and at incubator temperatures (37 C) there is considerable variation in the stability of different preparations. At 56 C all samples lose considerable potency. Crystalline penicillin sodium, however, shows no detectable loss of activity after exposure to 56 C for 1 month or to 100 C for 12 hours Apparently, most of the salts except the ammonium salt have essentially the same stability as the sodium salt. Solutions of penicillin prepared for clinical use can probably be kept at room temperature (22 C) for 1 week without evidence of deterioration and some lots remain fully active for 10 to 12 days At 37 C., however, the full potency of solutions persists for only 4 days.

Methods for Assaying Penicillin

Fleming's original observation on the clear zone around the growth of the mold in which staphylococci failed to grow has been the basis of most of the commercial assay methods. He employed a serial dilution method to test the activity of his crude broths. He also used a "gutter and streak" method and then an "agar cup" technic All of these involve the principle that penicillin diffuses out to the agar either from the gutter or from a porous cup placed on the agar and the potency of the penicillin is proportional to the diameter of the clear zone around the original deposit of the penicillin solution.

In the most widely used commercial method a base of nutrient agar is hardened at the bottom of a Petri dish and is then inoculated with a warm agar suspension of the test organism, generally a standard culture of Staphylococcus aureus. This agar, too, is permitted to harden, after which a number of small cylinders are dropped lightly on the surface where they form watertight cells. Dilutions of the penicillin of unknown potency are then pipeted into some of the cylinders and a known, standard penicillin is put into one or more of the others. During the incubation, penicillin diffuses out of the bottom of the cylinders into the agar and the bacteria meanwhile begin to grow. Within 4 to 7 hours the inhibition zones become obvious and the plates are usually read at 16 hours. A formula correlating the diameter of the zone of inhibition with the concentration of penicillin permits the construction of a standard curve and the unknowns are read from this curve. This method has the disadvantage that the diameter of the clear zone is affected by many variables so that it is always essential to have a reference standard of penicillin to compensate for these errors and to permit greater reproducibility of the results.

There are numerous modifications of this method. Some involve filter paper discs or holes cut in the agar instead of the cups. Refinements in assay, such as guides for placing the cylinders on the plates and specially ruled platforms for reading the diameters of the inhibition zone, have increased the efficiency and accuracy of the methods. Some laboratories have substituted other organisms such as Bacillus subtilis for the Staphylococcus aureus.

Serial dilution methods, while more cumbersome and usually requiring sterile technic, which are not essential in the previous methods, have a definite field of usefulness. The test organism in the method most commonly used for these purposes is a group A hemolytic streptococcus, and hemolysis of red blood cells is used as a guide to distinguish between growth and inhibition. Rapid methods have been recommended which utilize the formation of hemolysin as an indicator A simpler method employing a culture of B. subtilis has also been recommended for clinical use.

Other technics, involving measurement of the light transmission of broth cultures to which penicillin had been added, are also used. Such turbidimetric methods, which have the advantage that the end point is measured with the aid of a photoelectric turbidimeter thus reducing one of the sources of error, are more rapid and less cumbersome than serial dilution methods and reasonably accurate results can be obtained quite rapidly.

The Oxford unit of penicillin as originally defined was "that amount of penicillin which when dissolved in 50 cc of meat extract broth just com-

pletely inhibited the growth of the test strain of Streptococcus aureus." Later a moderately pure calcium salt of penicillin was carefully compared by a number of laboratories and has been set up as a "reference standard." Smaller quantities of the latter are frequently distributed to those who require the use of standards. The potency of the crystalline master standard was originally fixed at 1,650 units per milligram and of the reference standard at 370 units per milligram.

At an international conference on penicillin held in October, 1944, under the auspices of the Health Organization of the League of Nations, the crystalline penicillin G was adopted as the international standard and the international unit of penicillin was defined as "the specific penicillin activity contained in 0.6 microgram of the International Penicillin Standard." The calcium salt reference standard of the Food and Drug Administration was adopted as the International Penicillin Working Standard and its activity was defined in relation to the International Penicillin Standard so that 2 7 micrograms of the International Working Standard contain 1 International Unit of penicillin. These are fairly close to the previous values mentioned.

Salts and Esters At least seven different penicillin salts and several esters have been produced. The toxicity of the salts of penicillin seems to be due primarily to the cations used in their preparation. Only two of the salts, namely the sodium and the calcium salts, are being made on a commercial scale. There is essentially no difference in the toxicity of these two preparations, but the calcium salt is less hygroscopic and possibly somewhat more stable on that account. For that reason most of the oral preparations and those in which penicillin is prepared for topical application employ the calcium salt. The commercial preparations intended for parenteral use are prepared as a sodium salt

Several esters of penicillin have been prepared and their properties have been described They seem to be less active *in vitro* but retain their activity *in vivo*, probably due to the liberation of active penicillin by hydrolysis. A benzyl ester is said to be more active than sodium penicillin in experimental infections of mice when given by injection and highly active when given by mouth.

Forms of Penicillin A number of distinct forms of penicillin have been identified in cultures of Penicillium notatum Three of these are known as penicillin F, G, and X in this country and as penicillin I, II, and III, respectively, in Great Britain These have been isolated in crystalline form. Other active substances have also been described which differ from these three in that they are probably protein in nature, nondiffusible, active only in the presence of glucose, and are effective against gram-negative as well

as against gram-positive bacteria. The latter substances have been variously called notatin, penatin, "second factor," and penicillin B, but they are all closely related, and may be the same substance. Commercial penicillins which are prepared from deep-vat cultures consist almost entirely of penicillin G, but those prepared from shallow-surface cultures in flasks and purified by chloroform extraction may contain appreciable amounts of penicillin X, varying up to 20 and 25 per cent. Methods of obtaining high yields of penicillin X from submerged cultures have also been devised recently

Chemically, all penicillins—F, G, and X and still another, recently revealed form, K—have the empiric formula $C_9H_{11}O_4SN_2 \cdot R$. In penicillin F, R is Δ^2-pentenyl, $—CH_2 \cdot CH{=}CH \cdot CH_2 \cdot CH_3$; in dihydropenicillin F, R is *n*-amyl; in penicillin G, R is benzyl; in penicillin X, R is *p*-hydroxybenzyl; and, in penicillin K, R is *n*-heptyl. The structure of penicillin B is not known and is probably much more complex.

The four known molecular species of penicillin vary significantly in their bactericidal activity *in vitro*. Thus, referred to penicillin G as 100, the relative activities per milligram of penicillins F, G, K, and X are 90, 100, 140, and 55, respectively (1,550, 1,667, 2,300 and 900 units per milligram) against Staphylococcus aureus, 82, 100, 120 and 140, respectively, against the C203 strain of hemolytic streptococcus; and 53, 100, 75, and 50, respectively, against a cultured strain of Spirochaeta pallida (Reiter). Penicillin K is inactivated in the body to a greater extent and is more rapidly excreted than F, G, or X, resulting in far lower therapeutic activity than might be anticipated from its activity *in vitro*. In the treatment of experimental syphilis in rabbits and in pneumococcic and hemolytic streptococcic infections in white mice, penicillin K is only 9 to 15 per cent as active as penicillin F, G, or X Poor clinical results in the treatment of syphilis have been traced to the high penicillin K content in many commercial preparations of penicillin, and vigorous steps are now being taken to eliminate this form and to include only penicillin G in the commercial products released for clinical use

The potency of crystalline penicillin X is approximately 900 units per milligram, while that of penicillin G, as already noted, is 1,650 units per milligram (actually 1,667 units by definition of the International Standard). Penicillin X has been found to be more effective *in vitro* against a strain of type A Friedlander's bacillus and against a strain of Bacillus cereus. It was also found to be 3 to 5 times more effective than penicillin G in protecting mice against infection with type I pneumococcus. Preliminary observations in the treatment of gonorrhea suggested that it was significantly more effective when used in small doses Consistently higher

blood levels of penicillin X, using Bacillus subtilis as a test organism, were maintained during the first 2 hours after intramuscular injection and it was excreted into the urine somewhat more slowly than commercial preparations.

Recent findings suggest that comparable therapeutic results may be expected with smaller doses given at the same intervals, or with the same dose given at longer intervals, when penicillin X is used. The latter has been found to be nontoxic. There is also some evidence to suggest that it is less well absorbed than penicillin G after oral ingestion. Penicillin X has proved effective in various conditions, including subacute bacterial endocarditis, which had failed to respond to commercial penicillin in large doses.

Since the tendency has been to produce increasingly pure preparations, there is a possibility that the newer products may vary in the specificity of their action against different types of infection. The difference between the action of pure and of impure products against Treponema pallidum is a good example and suggests that some potent and perhaps specific antibiotic activity may be discarded during the process of purification of penicillin.

Action on Bacteria

The early observations of Fleming indicated that penicillin has bacteriostatic, bactericidal, and bacteriolytic properties Others have since shown that penicillin tends to modify the cell division of sensitive bacteria, the changes consisting in an elongation of the bacterial cell and filament formation.

Under some circumstances blood or serum may enhance the action of penicillin In the case of meningococcus, this has been shown to be due to a heat labile factor, probably complement, but other immunity factors may also be concerned Enhancement by phagocytosis apparently is not a factor in its action Penicillin, however, is not toxic to white blood cells except in concentrations far beyond those ordinarily used Under certain circumstances serum appears to inactivate penicillin to some extent.

In the presence of adequate concentrations of penicillin, bacteria are destroyed fairly rapidly, much more so than with high concentrations of the active sulfonamides The rate of death of the bacteria depends largely on the concentration of penicillin In this respect it is similar to sulfonamide action but it differs from the latter in that within a fairly wide range it is not influenced by the concentration of organisms Apparently penicillin, like the sulfonamides, is not absorbed or destroyed in the process of bacterial inhibition.

Two alternative theories have been proposed to explain penicillin action.

The one assumes that the individual bacteria in any culture vary in their sensitivity and the graded doses of penicillin inhibit cells corresponding to their greater resistance The other considers all of the organisms to have the same sensitivity but that penicillin acts by prolonging logarithmically the generation time of every cell. Neither of these explanations is entirely satisfactory It does seem clear, however, that multiplication of organisms is necessary in order to establish penicillin effect. This is also true for the sulfonamides Possibly the penicillin acts by preventing the bacteria from completing their normal process of fission. Certain amino acids have been shown to enhance, others to antagonize the action of penicillin on gram-negative bacilli.

Penicillin Sensitivity

In general, the most gratifying clinical results have been obtained in those diseases in which the causative organism is susceptible *in vitro* to concentrations of penicillin which can readily be maintained in the patient and at the site where the bacteria are present and multiplying.

The exact concentration required to inhibit even the same strain, when determined by different observers, may vary, depending upon the methods, the media used, and other conditions under which the tests were carried out Generally, penicillin is most active under those conditions which are most conducive to rapid multiplication of the bacteria Unlike the sulfonamides, the constituents of favorable media do not usually contain substances which inhibit the action of penicillin Some inhibiting effect of serum on the action of penicillin has been noted On the other hand, fresh serum containing antibodies which are active without the mediation of living cells may interfere with the assay of penicillin levels in body fluids In the accompanying tables (Tables I, II) the various organisms and diseases are divided into those susceptible and those not susceptible, occasionally on rather scanty evidence.

Gonococcus This organism has been found to be the most sensitive of those studied. Furthermore, there was greater uniformity in the action of penicillin against strains of this organism than against most of the other common bacteria except perhaps the group A hemolytic streptococci. Lankford in a study of 203 cultures from 100 female patients found no resistant strains The extremes of tolerance which he observed range from 0 0025 to 0 02 unit per cc of culture All but a few of his strains were susceptible to 0 01 unit or less, which has been our experience, too All observers agree that both sulfonamide-susceptible and sulfonamide-resistant

strains are equally susceptible to penicillin. Some workers have succeeded in increasing the resistance of this organism to penicillin *in vitro*.

TABLE I

ORGANISMS AND INFECTIONS SUSCEPTIBLE TO PENICILLIN

Gram-Positive Cocci
- Staphylococcus aureus
- Staphylococcus albus (some strains)
- Anaerobic staphylococci
- Streptococcus haemolyticus (except Lancefield group D)
- Streptococcus viridans
- Nonhemolytic streptococci (most strains)
- Micro-aerophilic streptococci
- Anaerobic streptococci
- Pneumococcus
- Micrococcus tetragenus

Gram-Negative Cocci
- Gonococcus
- Meningococcus

Gram-Positive Bacilli
- Bacillus anthracis
- Bacillus subtilis (most strains)
- Corynebacterium diphtheriae (not in experimental infections)
- Diphtheroids (Corynebacterium pseudodiphthericum)
- Clostridium tetani
- Clostridium botulinum
- Organisms of gas gangrene
  - Cl welchii
  - Cl septicum (Vibrion septique)
  - Cl sporogenes (Bacillus oedematis maligni)
  - Cl. histolyticum
  - Cl sordellii
- Listerella monocytogenes (also other pathogenic varieties of Listerella)
- Lactobacillus acidophilus

Gram-Negative Bacilli
- Hemophilic organisms
  - Hemophilus ducreyi (variable results)
  - Hemophilus haemolyticus
  - Hemophilus influenzae (occasional meningeal strain of type b)
  - Koch-Weeks' bacillus
- Bacillus faecalis alcaligenes (some strains)
- Bacillus pseudotuberculosis rodentum
- Bacillus pullorum
- Other gram-negative bacilli (typhoid, paratyphoid, dysentery, proteus and brucella—some strains slightly sensitive to high concentrations *in vitro*)

Spirochetes, Spirillae, and Vibrios
- Treponema pallidum (syphilis)
- Treponema pertenue (yaws)
- Vincent's spirochetes (fuso-spirochetes)
- Borrelia recurrentis (European relapsing fever)
- Borrelia novyi (relapsing fever)
- Spirillum minus (rat bite fever)
- Spirillum rubrum
- Leptospira icterohaemorrhagiae (Weil's disease, most strains)
- Leptospira canicola
- Spirillum cholera (Vibrio comma) (most strains)

Fungi, Yeasts, etc.
- Actinomyces bovis
- Streptobacillus moniliformis (Actinomyces muris, Haverhillia multiformis) (rat bite fever)
- Erysipelothrix rhusiopathiae (swine erysipelas)
- Cryptococcus hominis (systemic blastomycosis)

Viruses and Rickettsias
- Psittacosis
- Ornithosis
- Meningo-pneumonitis
- Murine typhus

(Large doses in mice or chick embryos, no clinical confirmation)

- Trachoma (?)
- Inclusion blenorrhea (?)

Hemolytic Streptococci Group A hemolytic streptococci have generally been found to be uniformly susceptible to penicillin Naturally resistant strains have not been encountered, but resistance has been produced *in vitro*

TABLE II

ORGANISMS AND DISEASES NOT SUSCEPTIBLE TO PENICILLIN

Gram-Positive Cocci

- Staphylococcus albus (some strains)
- Streptococcus faecalis (Lancefield group D)
- Sarcina

Gram-Negative Cocci

- Neisseria catarrhalis
- Neisseria flava

Gram-Positive Bacilli

- Corynebacterium acnes (Bacillus acnes)
- Bacillus subtilis (some strains)
- Kurthia zenkeri (related to proteus group)

Gram-Negative Bacilli

- Enteric organisms (some strains are [illegible]
- [illegible]
- Bacillus paratyphosus and other salmonella
- Klebsiella pneumonia (Friedländer's bacillus)
- [illegible]
- Pasteurella pestis (plague)
- Pasteurella tularensis
- Brucella abortus (undulant fever)
- Brucella melitensis (undulant fever)
- Aerobacter aerogenes (Bacillus lactis aerogenes)
- Proteus vulgaris
- Bacillus faecalis alcaligenes (most strains)
- Pseudomonas aeruginosa (Bacillus pyocyaneus)
- Serratia marcescens (Bacillus prodigiosus)
- Pseudomonas fluorescens
- Morax-Axenfeld bacillus

Acid-Fast Bacilli

- Mycobacterium tuberculosis
- Mycobacterium leprae

Spirochetes, Spirillae, and Vibrios (see Table I)

- Leptospira icterohaemorrhagiae (some strains)
- Spirillum cholera (Vibrio comma) (some strains)

Fungi, Yeasts, Molds, etc.

- Monilia albicans
- Monilia candida
- Monilia krusei
- Blastomyces
- Coccidiodes immitis
- Sporotrichia
- Histoplasma capsulatum
- Other pathogenic and saprophytic fungi
- Yeasts
- Molds
- Pleuropneumonia organisms

Protozoa and Other Parasites

- Plasmodium vivax
- Plasmodium malariae
- Endamoeba histolytica (amebic dysentery)
- Trypanosoma
- Toxoplasma
- Filaria
- Trichomonas vaginalis
- Schistosoma

Rickettsial Diseases

- Rocky Mountain spotted fever
- Epidemic typhus
- Scrub typhus

Virus Diseases

- Mumps
- Measles
- Encephalitis (St. Louis)
- Equine encephalomyelitis
- Poliomyelitis
- Venereal lymphogranuloma
- Vaccinia
- Smallpox
- Influenza A and B
- Yellow fever
- Rabies
- Infective hepatitis (Catarrhal jaundice)
- Chickenpox

Diseases of Varied or Unknown Etiology

- Hodgkin's disease
- Acute and chronic leukemia
- Lupus erythematosus disseminatus
- Granuloma inguinale
- Infectious mononucleosis
- Rheumatic fever
- Pemphigus (most cases)
- Ulcerative colitis
- Rheumatoid arthritis
- Primary atypical pneumonia (virus pneumonia)
- Nonspecific iritis and uveitis
- Cancer

and has occasionally been found to increase during therapy. All the streptococci of the various Lancefield groups are susceptible except the group D (Streptococcus faecalis) strains which generally are found to be naturally resistant. Resistance of strains of Streptococcus faecalis obtained from urinary tract infections has also been noted, but some of these strains may be susceptible to the high concentrations of penicillin attainable in the urine during treatment. Most group A hemolytic streptococci have been found susceptible to somewhat less than 0.01 unit per cubic centimeter of culture.

Pneumococcus. Strains of type-specific pneumococci recovered from all sources seem to be susceptible to penicillin, although they show considerably greater variations in their sensitiveness as compared with the hemolytic streptococci. Most pneumococci require 2 to 4 times as much penicillin as do the hemolytic streptococci to inhibit growth. Here again there is no correlation between the specific type and the sensitivity of the different strains Naturally resistant strains of pneumococci have not been encountered, but the resistance of pneumococci has been increased experimentally. This increase in resistance did not alter the susceptibility of these strains to sulfonamides nor did it seem to alter the virulence The development of sulfonamide fastness had no effect on the response of strains to penicillin; and infections which on clinical grounds have been judged as being due to sulfonamide-resistant pneumococci respond as well as others to penicillin therapy.

Nonhemolytic Streptococci. Strains of Str viridans and of nonhemolytic streptococci have, in our experience, shown a susceptibility similar to that of pneumococci. Other workers have encountered naturally resistant strains Although subacute bacterial endocarditis seems to be an ideal condition for the development of resistance by these organisms in the course of treatment, only few instances have been reported where this has actually occurred One case of subacute bacterial endocarditis was encountered at the Boston City Hospital in which a strain obtained during a relapse following penicillin therapy was 4 times more sensitive than an earlier one obtained before that treatment was begun This may, of course, represent a reinfection with a new strain.

Meningococcus In our experience, the most susceptible strains of meningococcus have required 4 times the concentration of penicillin necessary to inhibit most of the strains of gonococcus, and the majority of the meningococci required from 8 to 32 times as much. Relatively resistant strains have been encountered This relative resistance of strains of meningococci has a parallel in the failure of some cases of meningococcic meningitis to

show a good clinical response to seemingly adequate treatment given both systematically and intrathecally Strains of each of the serologic groups have been tested and no correlation was found between the type and the sensitivity of meningococcus strains to penicillin.

The contrast between the gonococci and the meningococci with respect to their susceptibility to sulfonamides and penicillin is of some interest The gonococcus appears to be considerably more susceptible to penicillin; it is difficult to make it resistant *in vitro*, and naturally resistant strains or strains developing resistance during treatment have not yet been encountered On the other hand, the development of sulfonamide-resistant gonococci is now a common occurrence and indeed the majority of strains isolated from clinical cases of gonorrhea are now proving to be sulfonamide-resistant. The meningococcus is highly susceptible to sulfonamides and sulfonamide-resistant strains are extremely difficult to produce *in vitro*. Several cases of meningococcic meningitis have been considered on clinical grounds to be due to sulfonamide-resistant meningococci, but only one such case has been reported which seems convincing; unfortunately, *in vitro* studies were not recorded in that case

Staphylococcus Although most strains of staphylococcus are considered to be susceptible to penicillin, they show very wide variations in susceptibility. Strains are encountered which are from 2 to 264 times more resistant than the majority of strains of hemolytic streptococci. Some strains require concentrations which are difficult to attain by systemic therapy Naturally resistant strains have been encountered, and the development of increased resistance of previously susceptible strains both *in vitro* and during penicillin therapy has been reported Still greater variations occur among strains of Staphylococcus albus and of other nonpathogenic varieties of staphylococcus

In general, the strains of gram-positive cocci are susceptible; among the gram-negative cocci, the pathogenic varieties, namely meningococcus and gonococcus, are susceptible, whereas some of the nonpathogenic pharyngeal strains, such as Neisseria catarrhalis and Neisseria flava, are resistant. All the varieties of gram-negative bacilli are resistant to concentrations which can readily be obtained in systemic therapy and even to much higher concentrations, such as those used in local applications Certain strains of Hemophilus, however, are susceptible. Some strains of H ducreyi among the pathogenic varieties, and those of H. haemolyticus among the nonpathogenic ones seem to be about as sensitive as some of the strains of staphylococcus Occasional strains of type b H influenzae have been reported as being susceptible

Penicillin Inactivators

The ability to destroy penicillin is a property which is apparently widespread among bacteria, yeasts, and fungi. This property is not limited to organisms which are penicillin resistant. It has been shown that clarase, a diastatic enzyme, is a potent penicillin inhibitor, but its action apparently is not very rapid. Potent inhibitors have been obtained from other organisms, including several of the intestinal bacteria, anthrax bacillus, and Bacillus subtilis. Recently a stable and highly active penicillinase has been prepared from a paracolon bacillus. It has also been shown that cysteine is a potent pencillin inactivator which, under proper conditions, can act rapidly. Possibly other and simpler chemicals may also be effective in this respect. Penicillin inactivators are used primarily in the sterility tests which are required for all commercial preparations of penicillin and have proved highly useful for that purpose. As yet, there is no good evidence that it is of any great value in the control of therapy. Some heavy metals have also been shown to inactivate penicillin

Penicillin Fastness

In addition to the fact that bacteria vary in their susceptibility to penicillin, there may be considerable strain variation among organisms considered to be susceptible. Some strains of these organisms may be naturally resistant to relatively high concentrations of penicillin, as already noted in the case of Staphylococcus aureus In addition, strains of susceptible organisms may acquire resistance either *in vitro* or *in vivo* when exposed to subeffective concentrations of penicillin The development of penicillin fastness is not necessarily accompanied by the ability of the organism to produce penicillinase. Furthermore, the development of penicillin fastness is not accompanied by the development of resistance to sulfonamides or to other antibiotics, such as gramicidin. Conversely, the development of sulfonamide resistance or resistance to gramicidin does not alter the susceptibility of any organism to penicillin In a general way, the greater the susceptibility of any given strain to penicillin the more difficult it is to produce resistant strains *in vitro*, in experimental infections in animals, or in the course of treatment of human infections. Some enhancement of resistance, however, has been accomplished even in the highly susceptible strains of

ylococci, for example, when penicillin resistance develops *in vitro*, this property is apparently temporary and reversible. This, however, may not

be the case when resistance develops as a result of treatment of infections with subeffective doses. In either event, however, there is apparently some reduction in virulence of strains that have acquired resistance to penicillin. Sulfonamide resistance on the other hand is not easily reversible and may actually be a permanently acquired characteristic, and it is not accompanied by any change in virulence Development of penicillin resistance may be the result of a process of selection from mixtures of cells of varied susceptibility, the most susceptible being eliminated when exposed to the lower concentrations of the drug An alternative explanation would presume an alteration in the metabolic process of the bacterium and an adaptation which permits growth in the presence of penicillin such as probably occurs in the case of sulfonamide resistance

Influence of Other Agents

There is conflicting evidence concerning the combined effects of sulfonamides and penicillin. It is possible that a synergistic action between some of the sulfonamides and penicillin does occur with some strains of bacteria and not with others, which may account for the discrepancies. Clinical cases which purport to show a synergistic action must be accepted with reservation. Differences in distribution and penetration of sulfonamides and penicillin, as well as the possibility of differential inactivators, explain these clinical results Similar discrepancies occur with respect to the combined effects of penicillin and other antibiotics Whether or not they have any additive or synergistic effect, it has been shown that they do not have any interfering action. From a practical point of view, therefore, there is no contraindication to the combined use of penicillin and other antibiotics or sulfonamide drugs.

Pharmacology and Toxicity in Animals

Except for a few studies on acute toxicity, very few observations have been made on the pharmacology of penicillin in animals In the earliest studies no characteristic effects were produced either on the circulation or on the respiration These studies, however, are of limited value because of impurities present in the materials that were available at that time.

Van Dyke studied the properties of a pure crystalline sodium penicillin, and found that it is not hemolytic and does not alter the oxygen consumption of yeast cells, duck erythrocytes, or slices of rat liver. His material contained about 3,400 units per cc. Only slight reduction in the amplitude of the heart beat of the isolated frog's heart was noted with high concentrations, but this was reversible and there was no effect on the rate. No signifi-

cant effects were noted on the isolated uterus or ileum of the guinea pig, and the response of these structures to acetylcholine and posterior pituitary extract was not altered.

Penicillin is much less toxic to cells in tissue culture preparations than gramicidin, on a weight basis. In mice, the toxicity of the various salts of penicillin prepared from the same lot is approximately in the following order: sodium, ammonium, strontium, calcium, magnesium, and potassium. The toxicity of these salts appears to be due primarily to the cations used in their preparation. The acute toxicity of commercial preparations of sodium penicillin appeared to be related to the potency of the products in terms of units per milligram, the purer products having the least toxicity.

After a large intravenous injection of penicillin in dogs, the concentrations in body tissues and fluids were found, in decreasing order, to be as follows: kidney, small intestine, lung, buccal mucosa, bile, skin, liver, adrenals, pancreas, heart, voluntary muscles, and spleen. In the ocular tissues and fluids, the concentrations, in decreasing order, were as follows: extra-ocular muscles, sclera, conjunctiva, tears, chorioretinal layer, aqueous humor, vitreous, and cornea The measurement of penicillin concentrations in tissues, however, is quite unreliable Minor differences may be impossible to detect. Furthermore, there may be considerable individual variations The results also depend on the size of dose, the method by which it is administered, and the time after administration that the tissues are obtained

Absorption, Diffusion, and Methods of Administration

The early studies on the absorption and excretion of penicillin by Florey and Rammelkamp and their respective co-workers indicated that it is relatively inactive when given by mouth This was ascribed to the fact that the drug is largely inactivated by the hydrochloric acid of the gastric juice Rectal administration also was found to be ineffective because the drug was apparently inactivated by intestinal bacteria.

Studies on distribution of penicillin between the serum and red blood cells indicate that it fails to penetrate the red blood cells in significant amounts The average concentration found in erythrocytes is less than 10 per cent of the plasma concentration After systemic administration of penicillin in amounts comparable to therapeutic doses, the concentration found in the fluids and tissues of the eye are low and often not measurable by the usual methods of assay. It is necessary to use iontophoresis or a corneal bath in order to secure an adequate penetration of penicillin into the aqueous humor. Penicillin is excreted into the bile where it is usually found

in higher concentrations than in the blood. Penicillin has not been detected in human saliva, tears, gastric juice, pancreatic juice, and intestinal juice, at least after comparatively small doses. Its occurrence in body fluids and cavities during therapy are considered on pages 368–371.

The drug can be given conveniently by parenteral routes and it was found possible to inject solutions into various body cavities. Intravenous injections result in high initial concentrations of the drug in the blood plasma, but these concentrations fall rapidly until only traces can be found after 0.5 to 3 hours or slightly longer, depending upon the amount injected. Penicillin is rapidly absorbed when given intramuscularly; after subcutaneous injections it is absorbed more slowly and somewhat more irregularly. By using proper technics, penicillin can be recovered quantitatively from the urine after intravenous injection. Continuous bacteriostatic levels can be maintained in the blood more economically by doses of 15,000 to 25,000 units given every 2 or 3 hours than with much larger doses given at longer intervals.

Effective blood levels are maintained for somewhat longer periods after intramuscular than after intravenous injections of the same quantity of drug. Here again, higher initial levels are attained and effective levels are maintained longer, within certain limits, when the size of the dose is increased. The intramuscular route has proved to be the one of choice for routine treatment of patients. However, with more refined preparations the subcutaneous route may give results not much different from those obtained following intramuscular injections and without more discomfort.

Continuous Infusion. Administration of penicillin by a continuous infusion has the advantage of maintaining fairly constant blood levels as well as avoiding the discomfort of repeated punctures. The practical methods, however, require constant supervision. The intravenous method also necessitates injection of larger volumes of fluid than are sometimes desirable. In addition, constant intravenous injections, when continued for 2 days or longer, have given rise to thrombophlebitis in an appreciable percentage of the cases. This may frequently be obviated by the use of small amounts of heparin—not more than 1 or 2 units of heparin per cubic centimeter of penicillin solution. These small amounts of heparin are not sufficient to increase the clotting time of the circulating blood. Continuous intramuscular infusions are somewhat more difficult to regulate and are often quite painful but they may prove more satisfactory in practice.

Both of these methods, however, are difficult to carry out properly in patients who are acutely ill and uncooperative. Neither method has been adopted widely for routine use except when it is necessary to maintain

high levels over a long period or when frequent injections are not well tolerated. The serum levels maintained under constant infusion by either the intravenous or intramuscular route do not usually exceed the average concentrations obtained during intermittent intramuscular injections of the same total daily dose, but given every 2 hours, provided a large fluid intake is avoided. Although continuous infusions result in levels which are quite constant in any given patient, the concentrations with any given dose may vary in different patients. Some types of tubing used for infusions may inactivate penicillin to an appreciable extent.

Penicillin is actively excreted by the renal tubules. Patients with disturbances of renal function and those with considerable water retention usually require smaller doses to attain and maintain any given concentration in the blood. Penicillin blood levels may rise steadily during continued therapy in patients with anuria or marked nitrogen retention.

Patients receiving intermittent intramuscular injections who are on a moderate but unrestricted fluid intake and have adequate renal function usually have less than 0.03 per cent of penicillin per cc. of serum 3 hours after an injection of 15,000 or 20,000 units. About one-third of the patients will have these low levels even 2 hours after 15,000 units. Larger doses give higher and more sustained levels. In cases of congestive cardiac failure the concentration obtained in the serum 3 hours after a 15,000 unit injection may be comparable to that obtained 2 hours after a 25,000 unit injection in an ordinary case.

The bone marrow has also been utilized as the site of constant infusion of penicillin and may prove useful in some cases.

Enhancement and Prolongation of Penicillin Action

Penicillin suspended in oil was found to be more slowly absorbed, and effective concentrations could be maintained in the blood with such suspensions longer than with aqueous solutions. With the use of a beeswax-peanut oil base, it was found possible to maintain effective levels for 6 to 10 hours or longer. Cures of gonorrhea with single injections of 100,000 units in a 3 per cent solution of beeswax in peanut oil have been reported.

The early observation that patients with renal insufficiency maintained high blood levels of penicillin for several hours led to the use of artificial means for slowing excretion by applying the principle of "excretory blockade." It was noted that excretion of penicillin was depressed by the simul- [illegible] injection of diodrast. p-Aminohippuric acid is rapidly excreted by

[illegible] attempts to slow renal ex-

[illegible] on of p-aminohippuric acid,

together with penicillin, it was found possible in animals and in humans to attain and maintain significantly higher concentrations in the circulating plasma than is practical without the use of excessive amounts of penicillin. *p*-Aminohippuric acid has been found to be nontoxic to mice, rabbits, and dogs in the amounts necessary to produce this effect and the same has been shown to be the case in humans, at least when used for relatively short periods This type of therapy is obviously not a very desirable or practical one. While it may reduce the amount of penicillin needed, it does not obviate the objectionable use of constant intravenous infusions and adds to the difficulties in regulating the rate of injection by introducing another variable.

Bronfenbrenner and Favour attempted to accomplish the same purpose with oral administration of benzoic acid combined with fluid and salt restriction. Sodium benzoate proved less effective and somewhat more nauseating Simple restriction of fluid intake to 1,500 cc and of salt intake to 3 grams a day doubled the penicillin blood levels following interrupted intramuscular injections of penicillin Benzoic acid given in doses of 2 5 grams every 4 hours either with food or in capsules 20 to 30 minutes before the intramuscular injections doubled the penicillin blood levels when the patient was on an unrestricted diet. The combination of these two procedures resulted in a four- to eightfold increase in penicillin blood levels, thus permitting a wider spacing of the doses

A simple method of delaying absorption from ordinary intramuscular injections involves the use of local chilling by means of an ice bag placed over the site of injection This must be carried out for 1 or 2 hours before and may be continued for a period of 5 to 12 hours after each injection. A harness may be applied so as to keep the ice bag in place and the ice is changed every 3 or 4 hours With this method, it is claimed that effective blood levels may be maintained for 5 or 6 hours after a single injection of 50,000 to 100,000 units, and that acute gonorrhea may be cured by a single injection of 50,000 units The method, however, is cumbersome and does not seem feasible for prolonged therapy.

The addition of vasoconstrictive drugs to the penicillin, given in some medium in which it may be absorbed slowly, may result in further delay of absorption Adrenalin or some longer acting drugs, together with gelatin, have shown appreciable prolongation of the penicillin action These methods, however, have not yet received adequate clinical trials, particularly in severe infections which require the maintenance of significant blood levels over long periods Neither do they meet all the objections raised to parenteral therapy.

high levels over a long period or when frequent injections are not well tolerated. The serum levels maintained under constant infusion by either the intravenous or intramuscular route do not usually exceed the average concentrations obtained during intermittent intramuscular injections of the same *total daily dose*, but given every 2 hours, provided a large fluid intake is avoided. Although continuous infusions result in levels which are quite constant in any given patient, the concentrations with any given dose may vary in different patients. Some types of tubing used for infusions may inactivate penicillin to an appreciable extent.

Penicillin is actively excreted by the renal tubules. Patients with disturbances of renal function and those with considerable water retention usually require smaller doses to attain and maintain any given concentration in the blood. Penicillin blood levels may rise steadily during continued therapy in patients with anuria or marked nitrogen retention.

Patients receiving intermittent intramuscular injections who are on a *moderate but unrestricted fluid intake and have adequate renal function* usually have less than 0.03 per cent of penicillin per cc. of serum 3 hours after an injection of 15,000 or 20,000 units. About one-third of the patients will have these low levels even 2 hours after 15,000 units. Larger doses give *higher and more sustained levels. In cases of congestive cardiac failure the* concentration obtained in the serum 3 hours after a 15,000 unit injection may be comparable to that obtained 2 hours after a 25,000 unit injection in an ordinary case.

The bone marrow has also been utilized as the site of constant infusion of penicillin and may prove useful in some cases.

Enhancement and Prolongation of Penicillin Action

Penicillin suspended in oil was found to be more slowly absorbed, and effective concentrations could be maintained in the blood with such suspensions longer than with aqueous solutions. With the use of a beeswax-peanut oil base, it was found possible to maintain effective levels for 6 to 10

The early observation that patients with renal insufficiency maintained high blood levels of penicillin for several hours led to the use of artificial means for slowing excretion by applying the principle of "excretory blockade." It was noted that excretion of penicillin was depressed by the simul- [illegible] p-Aminohippuric acid is rapidly excreted by

tempts to slow renal ex-

of *p*-aminohippuric acid,

until intrathecal therapy was instituted In the absence of a block, diffusion of penicillin usually takes place from the lumbar into the cerebral subarachnoid space and into the ventricles as well as in the opposite direction.

Intraspinal injection of penicillin in normal persons and in meningitis patients may be followed by symptoms of increased intracranial pressure with headache, vomiting, stiff neck, and the appearance of pleocytosis and increased protein content in the spinal fluid The severity of the reaction usually depends upon the impurities in the preparation used and often increases with the amounts given With some of the highly purified preparations which have recently become available, it has been possible to give as much as 50,000 units or more in a single intrathecal injection without significant irritative effects. Severe reactions, including coma and vascular collapse, may occur after intraventricular administrations Severe reactions and convulsive seizures have also been observed following local applications of penicillin in neurosurgical procedures These reactions, too, may become less marked when more refined preparations are used in proper concentrations.

Diffusion from the subarachnoid space into the blood stream takes place at varying rates and is usually rather slow in normal individuals After doses of 10,000 units detectable amounts appear in the serum for a short time and can be recovered in the urine for 24 hours or longer. If more than 100,000 units are injected, bacteriostatic levels can be maintained in the serum for about 15 hours

Penicillin has been detected in the spinal fluid for 24 and sometimes as long as 96 hours after it was injected by the lumbar route, but occasionally it cannot be detected even after 14 hours After single intraspinal injections of 10,000 or 15,000 units, the concentrations in the spinal fluid 12 hours later may range from 10 to 160 units After 24 hours, the concentrations may vary from 5 units to the smallest detectable amounts, but occasionally as much as 80 units per cubic centimeter has been present. Small concentrations have been found in cisternal and ventricular fluid at autopsy 12 to 24 hours after a lumbar injection of as little as 10,000 units

Diffusion in and out of Pleural Cavity

During systemic therapy the concentrations of penicillin in pleural fluids are usually the same as or less than those found in the serum Levels ranging from 0 03 to 0 22 unit per cc. of pleural fluid has been obtained in patients under treatment with doses of 20,000 units, intramuscularly every 2 or 3 hours. The levels in the serum taken at the time of thoracentesis were

Absorption after Oral Administration

When a dose of 100,000 units was given on an empty stomach, the amounts excreted in the urine were found to be the same or larger than those following the usual single intramuscular injection of 15,000 to 20,000 units This suggested that the oral method is feasible, provided that large enough doses are used.

A number of antacids, buffers, capsules, and oils have been used in attempts to protect the penicillin from the acidity of the stomach. Wide variations in absorption of oral penicillin are found when the same substances are given to different individuals. Usually, from 3 to 5 or more times as much oral penicillin is required to achieve the results obtained by intramuscular injections. In the presence of achlorhydria there is more complete absorption from the stomach.

In many subjects, and even in achlorhydric individuals, large doses given with or shortly after a meal have failed to result in detectable blood levels when the same dose given half an hour before a meal gave appreciable and sometimes high levels There is some indication that ordinary penicillin as prepared for parenteral use in saline solution will give levels which are as high and as well sustained as most of the special oral preparations. The mixture of such solutions with aluminum hydroxide gel and possibly with other basic aluminum compounds may give somewhat better results than other forms Oral preparations have been used with some success in the treatment of gonorrhea, pneumococcic pneumonia, and in some other infections, but they are obviously unsuited for the treatment of severe infections which require the maintenance of high levels over long periods

Diffusion into Cerebrospinal Fluid

When penicillin is given by the intravenous or intramuscular route, it is not possible to detect significant amounts in the cerebrospinal fluid. Some workers, however, have found detectable concentrations, especially after very large doses, in cases of meningitis There is good clinical evidence that the concentrations of penicillin obtained in the spinal fluid in cases of bacterial meningitis treated systemically are probably not sufficient to control the infection Cases have been noted in which the clinical condition of the patient and the findings in the spinal fluid showed no improvement after several days of systemic penicillin therapy, to be followed by prompt improvement when intrathecal administration was tried There are also known cases in which meningitis first made its appearance during the course of treatment of extrameningeal infections by intramuscular or intravenous penicillin In these cases, likewise, there was no improvement

10,000 units into an infected knee joint This slow absorption from the synovial cavity has been suggested as a method of administering penicillin in order to obtain a prolonged systemic effect As much as 120,000 units has been injected into one intact, but infected knee joint and bacteriostatic concentrations were found in the serum up to 13 to 24 hours later. Penicillin has also been found in joint fluids during intravenous or intramuscular injection in concentrations about one-half of that found in the serum

Peritoneal Fluid. In infants and children, penicillin has been found in peritoneal fluids after intramuscular injection. It has also been found in the serum after intraperitoneal injections and after implantations into the peritoneum in cases of abdominal operations

Pericardial Fluid Penicillin has been detected in the fluid obtained by aspiration of the infected pericardial cavity during intramuscular therapy. After local injection of 20,000 or 25,000 units, the pericardial fluid may contain from 2 5 to 160 units per cc 24 hours later Penicillin, therefore, seems to diffuse out of the pericardial cavity rather slowly.

What has been said about the diffusion into and out of serous cavities is said to be true also for abscess cavities. Diffusion into and out of such cavities depends to a great extent on the localization of the abscess, the thickness of its wall, and the size of the cavity. The results obtained suggest that local instillation of penicillin into such cavities may be a highly desirable part of the treatment

Inhalation and Intratracheal Instillation

The feasibility of utilizing penicillin in the form of an aerosol from a nebulized solution has been suggested by the demonstration of penicillin in the lungs and urine of animals after inhalation It may be possible to recover as much as 60 per cent of penicillin administered to cooperative human subjects who inhale the penicillin aerosol directly from a nebulizer placed in the mouth. Clinical methods and apparatus for applying this procedure therapeutically have been developed and are being improved. When the penicillin is used in concentrations of 40,000 to 100,000 units per cc, from 10 to 20 per cent of the administered penicillin can be recovered in the urine, mostly during the first hour After such doses, the penicillin can be demonstrated in the serum for 1 hour and occasionally longer Penicillin has also been recovered in the blood and urine after bronchial instillations As much as 30,000 to 50,000 units may be used in a single daily application intratracheally through a bronchoscope. Penicillin has also been incorporated into iodized oil and instilled directly through a

usually from 2 to 8 times higher than the concentrations found in the pleural fluid.

Intrapleural injections into a noninflamed pleura are sometimes accompanied by transient pleural pain, fever, and pleocytosis. There are usually no ill effects from similar injections in cases of empyema. In such cases, the intrapleurally injected penicillin is absorbed rather slowly, so that considerable amounts may still be found in the fluid as long as 96 hours after the injection of a large dose. The amount found and the persistence apparently depend upon the amount of penicillin injected and on the nature and size of the cavity.

After a dose of 5,000 units intrapleurally, the penicillin usually cannot be detected in the blood serum, and after 10,000 units only small concentrations are found for a short time When larger amounts, from 30,000 to 240,000 units, are given intrapleurally, significant concentrations can be maintained in the serum for 6 to as long as 36 or 48 hours

The concentration of penicillin that remains in the pleural fluid at various intervals after intrapleural injections likewise varies considerably, irrespective of whether or not systemic therapy is being maintained In most instances, the pleural fluid contains between 0.1 and 5 units per cc 24 or 48 hours after injection of 50,000 to 100,000 units In some cases, the pleural fluid level may reach even lower concentrations than the serum levels obtained at the same time.

Some diffusion, therefore, takes place from the blood stream into the pleural fluid as well as in the reverse direction, but it is quite variable, the concentrations found in the pleural fluid after local instillations are also erratic. These variations are probably due to differences in the character of the pleural cavity and of the fluid Loculation of infected fluids may account for some of the wider discrepancies Although diffusion is poorest in and out of thick-walled pleural cavities and in those in which the fluid is thick, no definite or consistent correlation has been found between the specific gravity of the pleural fluid and the diffusion into it from the blood or from it into the blood These findings suggest that local instillation is an important feature of the penicillin treatment of empyema, and once the extrapleural infection is controlled, concomitant systemic administration of penicillin is less important than the local instillation

Diffusion in and out of Other Serous Cavities

Synovial Cavities. Reports on the diffusion in and out of body cavities other than the pleura and subarachnoid space are limited Small amounts have been measured in the serum for several hours after the instillation of

cc per day. The total daily amount may be dissolved in that volume and the flow regulated accordingly.

Penicillin in Oil and Wax. Suspensions of calcium penicillin in a menstruum of refined peanut oil in which white wax is dispersed have also been released for sale They are packaged in concentrations of 100,000, 200,000, and 300,000 units per cc The 100,000 and 200,000 unit preparations contain not less than 3 per cent white wax, the 300,000 unit preparations not less than 4.7 and not more than 4.9 per cent The calcium penicillin used in the 300,000 unit per cc preparations has a potency of not less than 900 units per milligram, that of the other concentrations a potency of not less than 750 units per milligram.

The indications for the use of these preparations are given as: gonorrhea, acute staphylococcic and streptococcic infections, and pneumonia A minimum of 300,000 units per day is required in these conditions. The 200,000 unit preparations may be administered at 12 hour intervals, but the 100,000 unit preparations must be administered at 8 hour intervals. Rotation of the site of injection is desirable; the upper, outer quadrant of the buttocks, the thighs, and the triceps are suggested sites

Oral Products The tablets and capsules of penicillin contain one or more of the following buffer substances: sodium citrate, sodium benzoate, aluminum hydroxide, calcium carbonate, magnesium oxide and aluminum dihydroxyaminoacetate The potency of each tablet or capsule is not less than 20,000 units and each package must contain not less than 300,000 units The tendency now is to produce tablets of 50,000 units each.

Capsules of penicillin in oil contain a suspension of sodium penicillin or calcium penicillin in refined vegetable food oil. Each capsule must contain not less than 20,000 units and each package must contain not less than 300,000 units.

Penicillin is also packaged as a combination of sodium penicillin or calcium penicillin and aluminum hydroxide gel, 30 cc. of the latter for every 100,000 units. The oral penicillin preparations should be administered on a fasting stomach but not less than 30 minutes before and not less than 1 5 to 2 hours after eating

Topical Products. Penicillin ointment has been made available in the form of calcium penicillin in a base composed of wool fat, petrolatum or white petrolatum, or any mixture of two or all of these with or without liquid petrolatum, white wax, yellow wax, cottonseed oil or peanut oil, or any mixture of these substances Its potency is not less than 250 units per gram, and it should not contain more than 50 microorganisms per gram. Penicillin ointments are packaged in collapsible tubes containing not more

bronchoscope. Absorption from the lung when given in this manner is much slower. Favorable clinical results have been reported from the use of a penicillin spray produced by a hand bulb atomizer, but the cases were not well controlled

Topical Application

Penicillin has been applied locally in the form of solutions and powders either as such or mixed with sulfonamides. They have been applied locally in the treatment of infected or potentially infected wounds and burns as well as in the treatment of various skin lesions. They have also been sprinkled into the peritoneal cavity during abdominal operations. The absorption from such applications is extremely variable. Penicillin should not be used for irrigations since prolonged contact is necessary for the drug to be effective.

Products Available for Clinical Use

Parenteral Products. These are sodium penicillin and calcium penicillin, so purified and dried that the final product has a potency of not less than 500 units per milligram. They are sterile, nontoxic, and nonpyrogenic and have a moisture content of not more than 2.5 per cent. They are packaged in 100,000, 200,000, 500,000, 1,000,000, and 5,000,000 unit sizes.

The penicillin may be dissolved in small amounts of sterile, distilled, pyrogen-free water, in sterile isotonic solution of sodium chloride, or in sterile 5 per cent dextrose solution When large unit sizes are being used in hospitals, the contents of the ampule should be dissolved in water or saline solutions so that the final concentration is 5,000 to 50,000 units per cc., depending upon the circumstances in which it is to be used, and the solution should be made up freshly every day Solutions for local injection into cavities or for continuous parenteral injections may be diluted further, if necessary.

For intravenous injections, the dried powder may be dissolved in sterile isotonic solution of sodium chloride in concentrations of 10,000 to 50,000 units per cc In practice, the total daily amount is usually dissolved in 1,500 cc. of solution and the flow regulated so that it takes 24 hours to run out.

For intramuscular injection, the total volume of each individual injection may be small, usually from 10,000 to 50,000 units per cc of isotonic solution of sodium chloride. For constant intramuscular drip, 120,000 units in 250 cc is recommended. It may be difficult, however, to maintain a uniform flow by this route with less than a total volume of 500 or even 750

of penicillin solutions provide a uniform and high concentration in the circulating blood, whereas the use of intermittent intramuscular injections gives an undulating concentration with peaks occurring shortly after the doses are given. The greater the size of the individual intramuscular dose the higher will be the peak and the longer the period during which the inhibiting concentration can be maintained.

As to duration of treatment, this will vary with the nature of the disease and with the result of experiences in that particular condition. In acute infections, such as gonorrhea, the total duration of treatment need not be more than a few hours in most cases In pneumococcic pneumonia, also, the condition may be adequately treated within 1 or 2 days, but in this condition it has usually been found necessary to continue therapy for an additional 1 to 3 days after clinical improvement has occurred in order to avoid relapse. In staphylococcic infections, on the other hand, prolonged treatment is necessary and the same is probably true of chronic gonococcic infections, especially in women These two examples are cited because of the tendency to form multiple purulent foci which are not rapidly healed during the initial phases of treatment, even when fairly large doses are used. When local treatment of abscesses by surgical evacuation or by instillation of penicillin topically is not feasible, it may be necessary to continue administration of the drug until complete healing of the abscess has occurred The reason for this may be the failure of the penicillin to penetrate the abscess in adequate concentrations In the case of the sulfonamides, on the other hand, the failures were due in some measure, if not entirely, to the presence in the purulent exudate of substances which nullify the action of sulfonamides It is possible that some of the failures of penicillin treatment of such abscesses are due to the presence of secondary infection with organisms which have a similar effect in that they produce substances inhibiting the action of penicillin

Although systemic administration in chronic pulmonary suppuration has sometimes produced satisfactory results, the use of penicillin by inhalation over a long period may be even more satisfactory, it may or may not be combined with systemic administration. In local infections of the skin, mouth, or eyes, topical use of penicillin may be adequate, but where the lesions are associated with advancing infections of the underlying tissues systemic administration is advisable to supplement the topical therapy. The therapeutic results in infections showing a tendency to become chronic and to relapse, as now known, must be considered as tentative until a sufficient time has elapsed to permit a final evaluation. This is particularly true in syphilis and in subacute bacterial endocarditis.

than 1 ounce, except that ophthalmic ointments must not contain more than 1/8 ounce.

Topical penicillin is also supplied in the form of calcium penicillin, packaged as a fine powder in vials or in foil, in containers containing not less than 10,000 and not more than 50,000 units of penicillin. These are suggested for injection in the form of sterile solutions into postoperative mastoid cavities and into operative sites in cases of osteomyelitis. It is also intended for instillation as sterile solutions into pleural and joint cavities. Sterile dressings wetted with a solution containing 1,000 units per cc are suggested for superficial infections of the skin caused by organisms susceptible to penicillin.

Penicillin Troches. These are composed of sodium penicillin or calcium penicillin and may contain masticatory substances. Each troche contains not less than 500 units. Those containing masticatory substances must be labeled as "chewing" or "masticatory" above the name penicillin troches wherever that appears on the label. Their use is indicated in the treatment of Vincent's infection. One troche is allowed to dissolve in the mouth and this is repeated 2 or 3 times a day between meals, and more often if necessary. The masticatory troches are chewed 2 or 3 times a day or every hour or two when high concentrations are desired.

Penicillin is also provided in the form of *dental cones* composed of calcium penicillin; they may also contain sulfanilamide, or sulfathiazole, or both. Each cone contains not less than 500 units and not more than 50 microorganisms per gram. If a sulfonamide is incorporated, its quantity is not less than 0.032 gram per cone. These are used for insertion after tooth extraction or as a treatment for dry socket.

General Principles of Penicillin Administration

In a general way, the dosage should be so chosen that the concentration of penicillin available at the site of infection is sufficient to inhibit the infecting organism. It is also essential for the penicillin to act for several hours at least before an adequate or complete effect can be expected. From what has already been said concerning the diffusion of penicillin it should be obvious that the drug must frequently be applied topically, by injection into the spinal canal or into serous cavities, before some localized infections can be cured. The same is probably true in infections which tend to become localized and walled off in abscesses. In the selection of dosage for systemic administration, constant intravenous or intramuscular infusions

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one rarely encounters a patient receiving penicillin by constant intravenous injection for a week or more without some of the veins that have been used being thrombosed. It is hardly possible to keep a needle in a vein for more than 2 or 3 days without causing enough irritation to produce this effect. The site of injection should therefore be changed at the first evidence of such irritation, and a fresh needle and complete infusion outfit should be used when this is done. Occasionally, complicating embolic phenomena have resulted from these thrombosed veins

Thermal Reactions Chills followed by transient fever may be encountered. Usually this is caused by the presence of pyrogens in the vehicle in which the penicillin is dissolved, although some penicillin, particularly the cruder forms, may retain some pyrogenic substances, purity tests to the contrary. Such reactions are likely to be more frequent from intravenous injections. Sometimes they result from the use of cold solutions They are not usually of great significance, but they may be serious in severely ill patients who are on the verge of shock.

In the same general category are the headaches, flushing of the skin, and abdominal pain which sometimes accompany penicillin administration. These, too, are more frequent with intravenous therapy than following intramuscular injections Abdominal pain may sometimes be quite severe and colicky in character, often suggesting an acute surgical abdominal condition, and is more frequent among females. Usually, however, it is transient and of no known significance. In patients with bacterial endocarditis it may suggest the presence of embolic phenomena

Transient Azotemia. This has been mentioned by some observers. Significant rises in the blood nonprotein nitrogen as a result of penicillin therapy are probably quite rare. Occasionally, however, it may reach serious proportions, possibly in patients with underlying abnormalities of kidney function. One patient at the Boston City Hospital given oral penicillin had marked azotemia which persisted in spite of adequate fluid administration and was relieved only after the penicillin was discontinued. Sulfonamides in full doses were given without ill effect, and subsequent administration of penicillin also failed to reproduce the azotemia.

Cutaneous Manifestations. These are probably the most frequent untoward reactions. Urticarial eruptions have been noted in about 5 per cent of cases under continuous treatment for several days. In some instances similar eruptions have occurred some time after discontinuing penicillin therapy and resembled serum sickness in that respect. Cutaneous sensitization has been noted, some patients being sensitive to both crude and refined penicillin and others reacting to local injection only when crude

Clinical Use of Penicillin

Toxicity

The drug is generally considered to be innocuous and, as compared with other effective chemotherapeutic agents, it is essentially free of serious untoward effects Some toxic effects, however, have been observed, although usually they are not serious.

Local Reactions The most common untoward effect from penicillin therapy has been pain and discomfort at the site of the local injection This was more commonly observed and was more severe with earlier preparations Some of the more recent preparations are almost devoid of local irritating effects unless given in large amounts or in very high concentrations In general, pain may be reduced by avoiding subcutaneous injections and by reducing the volume of the individual intramuscular injections. With most of the penicillin now obtainable, it is possible to use up to 50,000 units per cc without much local pain As stated previously, the site of injection must be changed frequently—several sites being used in rotation; the most useful ones are the upper and outer quadrants of the buttocks, the outer aspect of the thighs, the triceps, and the deltoids The local irritation may possibly be reduced by cold applications at the site of the injection On the other hand, some of the local irritation results from the injection of cold solutions, since the vials of penicillin are usually kept in the refrigerator after the solutions are prepared Reactions from the latter source may be avoided by warming the penicillin in the syringe with the palm of the hand before the injection is made It must also be kept in mind that penicillin solutions are not self-sterilizing and that sterile technic must be employed in handling the preparations Colon bacillus abscesses have occurred at the site of single or continuous intramuscular injections, particularly in the thighs or buttocks

Continuous intramuscular injections are often associated with considerable pain. This may often be avoided by using a long enough needle for injections in the thigh It must be so fixed that there is little opportunity for it to move about freely The pain is most frequently noted when activity of the limb is followed by an increase in the rate of flow resulting in a rapid distention of the muscle, which is the cause of the pain

Phlebothromboses These are frequently encountered when penicillin is given by constant intravenous infusion Supposedly, this complication occurs more frequently when glucose solutions are used as a vehicle than with saline. Some observers with extensive experience have noted this complication in only 5 to 10 per cent of their cases, but in most general hospitals

thromboses which have been observed. The evidence, however, is not conclusive since the methods employed for demonstrating this effect are open to question No change has been noted in the blood platelets or in the prothrombin time. Penicillin has been shown to have a profound effect on the heparin tolerance of some patients, a slight effect in others, while in still others it has no effect whatever This has been offered as a possible explanation of the reported deaths from visceral hemorrhages in some cases of bacterial endocarditis treated with heparin and penicillin These observations, too, require confirmation with the use of more refined technic, and their importance in the cases of endocarditis is certainly open to serious question.

A case of bilateral hydrarthrosis of the knees has been reported as a complication of prolonged penicillin therapy. Anderson also mentions 4 cases of footdrop probably resulting from the injection of irritating preparations of penicillin along the course of nerves.

In patients with latent or unsuspected syphilitic infections untoward Herxheimer's reactions, some of them very severe, may occur during the first day or two of penicillin therapy. Fever alone, a recrudescence of symptoms at the original site of infection, a rash, or meningeal and cerebral manifestations, including psychoses, have been observed. One should be on the alert to suspect underlying syphilis as a possible cause of such untoward manifestations.

Treatment of Bacteremia in the Absence of Endocarditis

The introduction of sulfonamide drugs brought about considerable improvement in the clinical results obtained in the treatment of infections accompanied by bacteremia In hemolytic streptococcic infections the reduction of mortality was particularly striking, and in pneumococcic pneumonias associated with bacteremia the results have also been quite gratifying. In these conditions sulfonamide therapy reduced the mortality to perhaps one-fourth of what was formerly encountered. The results of sulfonamide treatment in staphylococcic bacteremias, however, were not nearly so striking and it is penicillin that has brought the greatest improvement in these cases

Well over 300 cases of infections other than bacterial endocarditis associated with blood stream invasion have been reported The great majority have been cases of staphylococcic bacteremia but a large number of streptococcic and pneumococcic bacteremias have also been reported. More than 70 per cent of the cases of staphylococcic bacteremia have been favorably affected by penicillin Many of the failures occurred during the

preparations are used. While this sensitization sometimes is associated with sensitivity to Penicillium and other molds, the allergy to penicillin is not necessarily accompanied by such sensitization. On the other hand, some individuals who are sensitive to molds are also sensitive to crude preparations of penicillin, while the more recent pure preparations seem to be well tolerated even in large doses by some of these individuals. A tuberculin type of sensitiveness has been demonstrated in one case in which there was a history of previous exposure to molds, but other cases have been described in which allergy to penicillin has been entirely independent of sensitivity to the spores of Penicillium. Since penicillin inhalation is now being advocated in the treatment of asthma, the possibility of sensitization or of reactions to the inhaled penicillin in this highly concentrated form must be borne in mind.

Cases of vesicular eruptions or bullous lesions, and occasionally exfoliative dermatitis, have also been described as occurring during or after penicillin therapy, as well as contact dermatitis from handling penicillin preparations or from its topical use.

The effect of re-administration of penicillin varies. In some instances a rash followed the first injection in patients who had previously been treated without any observed cutaneous reactions. On the other hand, most patients who develop urticarial or other rashes during penicillin therapy fail to manifest similar rashes when the drug is re-administered.* In cases of serious infection it is usually possible to continue therapy in spite of the skin eruptions, but the danger of serious bullous and exfoliative dermatitis must not be forgotten.

Cerebral Irritation and Convulsions These manifestations have been

This was thought to be due to the action of the penicillin rather than to impurities in it, since the reactions do not occur when preparations are subjected to conditions which inactivate the penicillin.

Hematologic Manifestations There is no evidence that penicillin is toxic to the erythrocytes or leukocytes Eosinophilia has been reported occasionally, and may represent a response similar to the delayed skin

* Contrary to the experience of the Editor

because localized blocks have developed. Therapy may also fail because residual, walled-off pockets of fibrin or pus may have developed into which the penicillin may not penetrate in adequate amounts The crude earlier preparations gave rise to considerable irritation of the meninges and this may have accounted for a certain number of cases of block which, in turn, led to failure of treatment. It should now be possible to give larger amounts with much less irritation, and better results may be anticipated

Because of the better diffusion of sulfonamides into the cerebrospinal fluid, combined treatment with sulfonamides and penicillin, given both systemically and intrathecally, is recommended in all cases of meningitis due to penicillin-susceptible organisms. In addition, cisternal, intracerebral, and sometimes intraventricular injections of penicillin may have to be used when the cerebrospinal fluid fails to become sterile or block develops Some cases have been reported in which meningitis was cured by systemic penicillin therapy without resort to intrathecal administration, but these are few and it is hard to exclude the role of sulfonamides in the recoveries.

The results in meningococcic meningitis have been quite varied. Sulfonamide drugs alone have been notably successful, reducing the mortality to a very low level (averaging 5 to 10 per cent) Occasional cases have been reported, however, in which relapse or failure to improve on sulfonamide therapy was followed by improvement when penicillin therapy was given systemically and intrathecally The reverse, however, has also been true and, in our experience, has been more frequent. Some patients who continued to remain febrile and even failed to show an adequate bacteriologic response under penicillin given both intramuscularly and intraspinally showed rapid improvement when treatment with sulfonamides was undertaken. In such cases, it was demonstrated that the strains of meningococcus were not highly susceptible to penicillin

A few cases of fulminating meningococcemia, which clinically seemed to fit the Waterhouse-Friderichsen syndrome, are reported as having recovered after treatment with penicillin Most of these patients, however, received many other types of therapy, including sulfonamides, corticoadrenal preparations, and stimulants, in addition to penicillin The exact role of the penicillin in the recovery of these cases cannot, therefore, be evaluated, nor can the diagnosis in most of them be accepted without question.

In pneumococcic meningitis, too, the results have been far from uniform The general recovery rate is between 40 and 50 per cent, even in cases in which sulfonamide therapy is used in addition to intrathecal and systemic penicillin. This, however, compares favorably with the recovery rates

early trials of penicillin therapy and resulted from the use of relatively small doses and of short periods of treatment. It is now recognized that prolonged and intensive treatment is needed in many cases of staphylococcemia, especially when this condition is associated with multiple foci of infection or when the organism is not highly susceptible.

The results in cases of hemolytic streptococcic septicemia have been more striking, the mortality in these cases being less than 10 per cent. Good results have been obtained in cases of puerperal infection, including some with blood stream invasion by anaerobic streptococci.

The effects of penicillin in pneumococcic bacteremia is quite dramatic, [illegible] dition or until serious and extensive purulent complications have already developed, while others, particularly in pneumococcic infections, are associated with serious underlying disease.

Penicillin dosage in bacteremia depends upon the organism and the nature of the underlying condition In general, however, treatment should be more intensive and more prolonged than in cases without bacteremia In pneumococcic bacteremia in which focal purulent complications have not yet developed, treatment need be continued for only 2 or 3 days after evidence of acute infection has subsided In staphylococcic and streptococcic infections, particularly the former, treatment should continue much longer, up to 1 or 2 weeks after fever or other evidence of active infection have cleared. When bacteremia is suspected, it is advisable to begin treatment with either constant intravenous or intramuscular injections, or with an intravenous injection followed by intramuscular injections at 2 or 3 hour intervals, using larger doses than would ordinarily be employed in similar infections without suspicion of bacteremia.

Treatment of Meningitis

Although most of the organisms commonly found in meningitis are susceptible to penicillin, the results of penicillin therapy in this condition have been much less satisfactory than in other types of infections with the same organisms This may be due in part to failure of the drug to enter the [illegible]

ventricular fluid In some cases, however, this circulation is inadequate

because localized blocks have developed. Therapy may also fail because residual, walled-off pockets of fibrin or pus may have developed into which the penicillin may not penetrate in adequate amounts. The crude earlier preparations gave rise to considerable irritation of the meninges and this may have accounted for a certain number of cases of block which, in turn, led to failure of treatment. It should now be possible to give larger amounts with much less irritation, and better results may be anticipated

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averaging about 35 per cent in cases treated with sulfonamide drugs before the introduction of penicillin. Considerably better results have been reported by some observers in small selected groups of cases treated with penicillin and sulfonamides combined, but this has also been true in cases treated with sulfonamides alone.

Treatment of streptococcic meningitis with sulfonamides has shown very favorable results. The number of cases treated with penicillin alone or with the combination of penicillin and sulfonamides is too small to determine to what extent the improvement is the result of adding penicillin. The mortality has undoubtedly been reduced in these cases. In the very severe cases in which treatment has been delayed the immediate improvement is probably more rapid and more striking when penicillin is used.

Staphylococcic meningitis does not occur very frequently. Some favorable results have been reported in patients treated with sulfonamides, but in general, therapy with these drugs has not been very effective, penicillin treatment being much more successful. The mortality is still high, probably more than 50 per cent even with intensive penicillin and sulfa therapy.

One discouraging feature of penicillin therapy in meningitis, particularly noticeable in cases due to pneumococcus and staphylococcus, is the tendency to relapse after apparent improvement. Previously, when such relapses were encountered in cases treated with sulfonamide drugs alone, they were almost invariably fatal, but under treatment with penicillin, particularly when combined with sulfonamides, recoveries have been noted in spite of such relapses.

There are reports of recoveries in some cases of meningitis associated with cavernous sinus thrombosis. Some of the most striking results have also been reported in cases of meningeal infections complicating head injuries, in which penicillin treatment supplemented adequate surgical management, while some cases of meningitis complicating otitic infections have responded completely without surgical intervention and with apparent clearing of the local infection at the same time.

In general, penicillin therapy is indicated only in meningitis due to sensitive bacteria. Occasional recoveries, however, have been reported in cases of influenza bacillus meningitis. In these cases, the organism was found to be sensitive to concentrations higher than those usually maintained in the blood but which are readily maintained in the cerebrospinal fluid after intrathecal injection. Since other gram-negative organisms have also been found to be sensitive *in vitro* to similar concentrations, the intrathecal therapy with penicillin supplementing sulfonamide therapy may be useful in other cases of meningitis due to gram-negative organisms ordinarily

classified as not susceptible. It is doubtful, however, whether infections with colon bacillus could be included in this category.

The principles to be borne in mind in the treatment of meningitis are (*1*) early maintenance of an adequate level of penicillin in the circulating blood and (*2*) introduction of penicillin directly into the subarachnoid space. In general, since sulfonamides are to be used at the same time, the usual precautions with regard to proper hydration of the patient are necessary before the first dose of sulfonamides, which is usually given by intravenous injection It may be advisable, however, to postpone sulfonamide therapy until after lumbar puncture to remove fluid for diagnosis and to permit intraspinal injection of penicillin, and after penicillin has been given intravenously and intramuscularly.

There is no full agreement as to the amount of spinal fluid to be removed or the dose of penicillin to be injected intrathecally It is probably best to allow fluid to escape slowly and to continue to drain as long as it will flow freely. The dose of penicillin is then introduced in a smaller volume of physiologic saline, so that the pressure is not raised above normal. The initial intrathecal dose may be 10,000 or 15,000 units, and can be given in a volume of 10 or 15 cc. During the first day or two, lumbar puncture drainage for penicillin instillation may be done at 12 hour intervals, depending upon the severity of the symptoms, the signs of meningeal irritation, and the height of intracranial pressure. When the symptoms of meningitis improve and the pressure drops, the injections may be given at 24 hour intervals until the number of cells declines to below 100 or 50 per cubic centimeter of spinal fluid and the smears and cultures remain sterile After that, a lumbar puncture need be done only if there is evidence of persistent infection and to ascertain that the fluid has remained sterile From 10,000 to 50,000 units of penicillin may be injected intraspinally after each puncture, and it can be given in a volume of 10 to 20 cc. or more.

If meningeal signs and purulent fluid recur, the intrathecal and systemic penicillin treatment as well as sulfonamide administration must be resumed, as though it were a new infection. Generally, systemic treatment with sulfonamides and penicillin is continued for about a week after the spinal fluid has become clear and sterile in most cases, and for 10 days to 2 weeks in cases of pneumococcic or staphylococcic meningitis The possibility of recurrence of infection may perhaps be diminished by continuing the sulfonamide therapy for 1 or 2 weeks after systemic penicillin therapy is stopped.

Treatment of Pneumonia

Because pneumococcic pneumonias have generally been treated successfully with sulfonamide drugs, very few of the early reports on penicillin therapy include large numbers of such cases. Some of these early reports, however, include small numbers of severe cases of pneumococcal pneumonia treated with penicillin either because the patients were extremely ill or because they failed to respond to sulfonamides. The results of treatment in these cases were most encouraging. A large number of cases have since been treated, but only a few reports of carefully studied cases are available

All observers have noted the rapid clearance of bacteremia in cases of pneumococcic pneumonia. It is often impossible to obtain positive blood cultures after the first dose of penicillin, except in some patients with focal infections or endocarditis. Subjective improvement and disappearance of signs of toxicity occur within a few hours and usually precede the fall in temperature. The results otherwise are generally quite similar to those obtained with adequate sulfonamide therapy. In some cases there is a critical drop in temperature within 8 to 12 hours after treatment has begun, but more frequently the temperature subsides over a period of 24 to 36 hours. There is often a secondary rise in temperature so that the patient may not be completely afebrile for 2 to 4 days after treatment has begun. Rusty sputum or pleuritic pain may continue during this period. It is usually difficult to obtain viable pneumococci from the sputum after the second day of treatment.

In our own experience, empyema or other focal infections have not developed after the start of adequate penicillin treatment. This complication, as well as pneumococcic arthritis, has been encountered in other clinics, but it is not always possible to determine whether they developed during therapy or were present before treatment started Such complications may, however, arise in severe cases when small doses are used or where the treatment is stopped too soon

In the early use of penicillin in pneumococcal pneumonia, attempts were made to determine the effects of small doses. Treatment with 4 doses of 10,000 units at 3 hour intervals resulted in frequent relapses; the same was true in cases treated with 3 or 4 doses of 100,000 units at 3 hour intervals In general, to avoid relapses it has been found necessary to maintain treatment at 3 or 4 hour intervals for 1 to 3 days after the temperature has reached normal Doses of 15,000 units every 3 hours, or 20,000 units every 4 hours, are usually adequate in cases of pneumococcic pneumonia In the severest cases, it is best to start with an intravenous injection and to give doses of 15,000 or 20,000 units at 2 or 3 hour intervals during the first 12 to

24 hours. If the fever persists after 3 days of adequate treatment, a search must be made for purulent foci. When the presence of fluid in the pleura is detected, aspiration and local instillation of penicillin are indicated. Occasionally, in severe cases infection may persist as a result of necrosed areas and abscess formation in the lung; prolonged systemic treatment is then indicated, and inhalation therapy may prove even more effective.

Cases of hemolytic streptococcic or staphylococcic pneumonia likewise respond favorably to penicillin treatment. Such cases, particularly those due to staphylococcus, require more intensive and more prolonged therapy. In streptococcic pneumonia doses of 120,000 units or more per day given in 6 to 8 doses intramuscularly are usually adequate. In staphylococcic pneumonias, 160,000 to 300,000 units given in doses at 2 or 3 hour intervals may be necessary. Since multiple abscesses are usually present in these lungs treatment is continued for 2 or even 3 weeks after the temperature subsides in an attempt to obtain complete healing. If the infection extends into the pleura, aspiration and instillation of penicillin are necessary. In streptococcic infection such treatment alone may result in complete cure. In staphylococcal infection, however, the tendency to pocket formation may interfere with completely successful therapy and surgical drainage may eventually be necessary.

Pneumococcic and staphylococcic pneumonias have also responded favorably to penicillin inhalation therapy. The results are as dramatic as those obtained by systemic treatment, and sometimes even more so Inhalations are given at 3 or 4 hour intervals, doses of 25,000 to 40,000 units in 1 cc. being used for aerosolization in each inhalation With this treatment also, sensitive organisms disappear rapidly from the sputum.

The role of immunity in the penicillin treatment of pneumococcic pneumonia has not received adequate study It is possible that the effectiveness of small doses in some cases of pneumonia may be due to an immunity which tends to enhance the penicillin action. This seems to be the case in experimental animals; there is no evidence, however, that penicillin interferes with the development of antibodies following its use in the treatment of patients with pneumonia

Some cases of psittacosis and ornithosis and of atypical pneumonias of unknown etiology have been treated with penicillin Although some of the authors have considered that penicillin influenced favorably the course of the disease, the results reported do not support this view. It is possible, however, that improvement in some of these cases occurred after the institution of penicillin treatment as a result of the elimination of secondary bacteriologic infections

Treatment of Staphylococcic Infections

Sulfonamide therapy in staphylococcic infections has not given entirely satisfactory results. Since the discovery of the action of penicillin was first made on staphylococcus cultures, it is quite natural that infections with this organism should have had the earliest and most intensive trials when preparations of active material became available. The results have indicated that penicillin is the most effective agent now available for the treatment of staphylococcic infections. Although there is no tally of the results obtained in cases of staphylococcic bacteremia since adequate supplies of penicillin have become available, the mortality is now probably less than 20 per cent.

Because of the nature of staphylococcic infections and their great tendency to form multiple foci of suppuration, the immediate improvement is not as dramatic as in pneumococcic infections. Furthermore, since the staphylococci are considerably less sensitive to penicillin than pneumococci, streptococci, and gonococci, larger dosages must be used and treatment must often be continued for much longer periods in order to bring and keep such infections under control.

It is worth bearing in mind, however, that the standardization of penicillin is generally based on tests employing standard strains of staphylococci, so that the activity of various preparations against these organisms should be quite uniform. This is in contrast to other infections, especially gonococcic and streptococcic infections and syphilis, in which results may vary because, unit for unit, these organisms are more susceptible to one form of penicillin or another.

Penicillin therapy in staphylococcic meningitis and staphylococcic pneumonia has been described (pp. 382, 385). Of the other staphylococcic infections the most common and the ones in which the most brilliant results have been obtained are osteomyelitis and carbuncles. According to Anderson and Howard, the rapidity of clinical improvement and extent of healing and repair of bone is greater in cases of acute osteomyelitis treated with penicillin alone than in those in which surgical drainage is also used. Abscesses of the soft tissues, however, should be drained. In suppurative arthritis there is danger of joint destruction unless penicillin is introduced directly into the synovial cavities, so that early surgery is indicated in order to provide for local instillation of penicillin into the involved joint once or twice a day. Treatment is continued for at least 2 or 3 weeks in acute cases, and severe ones with multiple lesions require even longer treatment. The clinical progress of the disease is used as a guide, since x-ray evidence of changes in the bone does not keep pace with actual progress. Not infre-

quently destruction of the bone has been most extensive at a time when clinical recovery was obvious. In such patients bone repair and the return to normal architecture usually continues during the next few weeks or months despite cessation of treatment. In cases treated early enough, signs of destruction sometimes cannot be demonstrated by x-ray.

The good results obtained in acute osteomyelitis are not limited to cases involving the long bones. Treatment has been highly successful in spreading osteomyelitis of the cranial bones, which may complicate sinus infections or follow trauma to or surgery of the skull. When sequestration occurs, surgical treatment must usually supplement penicillin therapy in order to obtain complete recovery. Some authors advise that surgical procedures be postponed until penicillin has been administered for at least 3 weeks and that all devitalized bone be removed at one time Treatment is then continued for another 2 or 3 weeks.

Penicillin has also been highly effective and has completely altered the prognosis in chronic osteomyelitis Arrest of infection with penicillin therapy takes place in a high percentage of these cases, thus allowing healing of both the bone and the soft parts. The chief cause of failures is associated with the development of penicillin resistance by the infecting organisms. The only measure deemed advisable in this situation is early, definitive surgical treatment, while the organism is still sensitive to penicillin. Immediate improvement with disappearance of all signs of infection occurred in 80 per cent of the cases treated at the Massachusetts Memorial Hospitals, but relapses occurred in almost half of them Positive cultures were obtained during these relapses, indicating that the infection had not been entirely eradicated. In the majority of the relapsing cases, sequestrums had not been removed and the reappearance of drainage was often associated with the spontaneous expulsion of sequestrums. In some cases relapses have been related to trauma, while in a few no cause was found. All of them, however, had massive fibrosis of soft tissues Almost all of the patients who remained well did not relapse, or had no visible sequestrums, or their sequestrums had been removed at the time penicillin was administered If adequate surgical treatment can be carried out where indicated while penicillin is being administered, the chances for arresting the infection are greatly increased Primary closure of operative incisions has proved extremely satisfactory. Furthermore, in the cases in which the cavities were not saucerized, there were no untoward effects, relapses, or failure to improve. Indeed, repair of bone and reduction in the size of the cavity seemed to take place more rapidly.

Mixed cultures are not infrequently encountered in chronic osteomyelitis.

The most frequent secondary organisms are beta hemolytic streptococcus and gram-negative bacilli. The streptococci usually disappear under penicillin treatment even more rapidly than the staphylococci. Gram-negative organisms, however, may sometimes interfere with the action of penicillin and result in persistent infection with failure of the sinus to heal. Staphylococci sometimes disappear from the cultures while penicillin is being administered and then re-appear after treatment. Marked improvement may take place in spite of this

In most cases 15,000 units given intramuscularly every 3 hours for 2 to 4 weeks is probably effective. The dose, however, should be controlled by the response of the lesions and the results of the cultures. If, after 4 to 6 days, the amount of drainage has not decreased or there is no reduction in the number of organisms in cultures of material from the local lesions, the dose should be increased to 25,000 units every 3 hours. As a matter of fact, the latter dose is probably advisable in all cases. In general, treatment of patients not requiring surgical operation is continued until 5 to 10 days after cultures become sterile. In patients requiring operation, penicillin is given for 4 to 8 days preoperatively and for 2 to 4 weeks postoperatively. It is apparently not necessary to continue treatment until the sinuses are completely healed, provided that the exudate has remained sterile for several days. The open sinuses usually persist for one or more weeks after treatment is completed and then heal satisfactorily.

Penicillin has proved highly effective in the treatment of large sloughing carbuncles of the type frequently encountered in diabetics. In such patients, penicillin reduces the need for the larger doses of insulin usually required in diabetes during severe infection. Early treatment may prevent diabetic coma Surgical drainage, however, is indicated in order to hasten healing. Direct instillation of penicillin into early carbuncles frequently results in rapid and sometimes dramatic improvement. Intramuscular injections alone are sometimes effective, but the additional local treatment may accelerate improvement. Solutions containing 1,000 units or more per cubic centimeter may be used for local injections or infiltrations.

Penicillin has also proved highly effective in multiple furunculosis, even in young infants Treatment is systemic, possibly supplemented with topical applications, and dosage is the same as for other staphylococcic infections.

Treatment of Streptococcic Infections

Some reports include direct comparisons of sulfonamide and penicillin therapy. Such studies indicate that after 2 or more days of treatment with

15,000 units of penicillin, intramuscularly, every 4 hours, hemolytic streptococci can no longer be found in the majority of throat cultures taken from patients with pharyngitis or tonsillitis. However, the organisms frequently reappear if the treatment has not been continued for 6 days and relapse and complications of the infection occur. With sulfadiazine, on the other hand, the number of positive cultures and the number of organisms in those which are positive are reduced while the treatment is being given, but hemolytic streptococci are again found in large numbers after treatment is stopped.

In scarlet fever, penicillin given intramuscularly during the eruptive stage and for several days longer may minimize or even eliminate the late septic complications. The causative organism does not reappear in nose or throat cultures, provided systemic treatment is continued for a full week or longer. Many of the postscarlatinal complications occur during the second week of illness or later, and have been shown by some workers to be due to organisms acquired by cross infection in open wards. These should be preventable by adequate treatment of all the patients, thus eliminating the sources of infection. Like the sulfonamides, penicillin does not influence the duration of the acute fever, toxicity, and rash, but the sore throat tends to disappear. There is a tendency for sore throat to recur in patients treated with penicillin for less than 6 days The drug has little or no effect upon the strictly toxic phase of scarlet fever, resembling sulfonamides in this respect, but the general condition of the patient seems to improve more rapidly when penicillin is used, especially in severe cases.

In erysipelas and cellulitis, improvement in the general condition of the patient is rapid, and the lesions do not spread after intramuscular treatment with penicillin is started The evolution of the cellulitis will depend upon the stage at which treatment is begun; if it is delayed, suppuration may occur Bacteremia is quickly controlled and regional adenitis clears fairly rapidly, but treatment should probably be continued until all evidence of infection has subsided in order to avoid recrudescences, particularly if suppurating areas have already developed which may constitute a source of reinfection

While penicillin is so highly effective in acute streptococcic infections and may eradicate the carrier state when adequate treatment is continued for a long enough period, there is now adequate clinical evidence to support the view that penicillin is ineffective in preventing rheumatic fever or in altering its course Rheumatic fever has developed in patients in whom the antecedent streptococcic infection has apparently been treated early or even in a subclinical state One group of observers even suggest that the clinical course of rheumatic fever may have been aggravated in some cases by treat-

The most frequent secondary organisms are beta hemolytic streptococcus and gram-negative bacilli. The streptococci usually disappear under penicillin treatment even more rapidly than the staphylococci. Gram-negative organisms, however, may sometimes interfere with the action of penicillin and result in persistent infection with failure of the sinus to heal. Staphylococci sometimes disappear from the cultures while penicillin is being administered and then re-appear after treatment. Marked improvement may take place in spite of this.

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contain substances which inhibit the action of the drug. In penicillin treatment such pocketing may cause poor penetration of the agent into the foci of infection.

The dramatic sterilizing effect of penicillin in acute gonorrhea is a result of its systemic, not its local, action Within a few hours after systemic administration, and even before the patient has voided any penicillin-containing urine, the organisms disappear from the urethral discharge in males. On the other hand, local instillation of penicillin into the urethra without systemic administration has failed to bring about bacteriologic cure.

The present tendency is to provide rapid treatment, and the ideal sought is the administration of a single dose, preferably by mouth Experience, however, has shown the need for continuous penicillin action over a period of at least several hours even in acute cases. Complications present at the time treatment is begun are important with respect to length of therapy. In some acute cases, the usual treatment of the acute infection without regard to the presence of complications has rapidly cleared up the complications as well as the local lesion. Many observers also have noted that such treatment eliminates the urethral or cervical exudate and the organisms but that the complicating epididymitis and certain other focal infections persist and run their usual course without recurrence of exudate or bacteria Signs of such focal complications may even first appear after an apparent symptomatic and bacteriologic cure of the gonorrhea On the other hand, focal infections have more often failed to respond when treatment has not been carried on for several days Even in such instances, the presence of localized purulent foci, particularly in the joints, has frequently failed to yield until penicillin was instilled locally. It would seem, therefore, that where local, deep-seated infections occur, prolonged systemic treatment is indicated, supplemented whenever possible by local injections In some patients with pelvic inflammation even prolonged treatment may be ineffective, because resistant bacteria have entered the infection It may be best in those cases to use both sulfonamides and penicillin and to continue treatment over a long period

There is universal agreement that there is no relationship between the sensitivity of gonococci to penicillin and the resistance of those organisms to sulfonamide drugs Clinically, sulfonamide-resistant cases have responded favorably to penicillin Indeed, most of the early cases were chosen for treatment with penicillin only because they failed to respond to adequate sulfonamide therapy

Dr Manson Meads and I have reviewed over 100 reports covering the treatment of more than 20,000 cases of gonorrhea, and have made certain

ment with penicillin. This had previously been noted for the sulfonamide drugs.

Infections with anaerobic streptococci have responded irregularly to penicillin treatment, due perhaps to the great variation in strain sensitivity among these organisms. Prolonged treatment may be necessary in such cases, particularly if there is an intravascular focus of infection, such as thrombophlebitis.

Data concerning the prophylactic use of penicillin in the streptococcic infections are rather scant. Its use has been recommended before and after dental manipulations in patients with rheumatic heart disease, in an attempt to prevent subacute bacterial endocarditis. There are no reports on the continuous use of penicillin, like the large-scale use of sulfonamides, in attempts to reduce the incidence and severity of acute respiratory infections and their complications. The use of penicillin lozenges, hard candy, or chewing troches which may have a prolonged action in the saliva has been suggested. Their purpose is to decrease the number of organisms in streptococcus carriers, thus reducing the spread of hemolytic streptococcic infections. One might predict that this large-scale use of penicillin for prophylaxis, if continued over a long period, might result in the development of resistant strains of pathogenic organisms. If strains which have become resistant in this manner can be shown to lose their virulence or eventually to return to a sensitive state, this may not be of any epidemiologic significance, but so far observations on this point are lacking.

Treatment of Gonococcic Infections

As already noted, the gonococcus is the most susceptible of the pathogenic bacteria. Thus far there have been no reports of naturally resistant strains, and there is even considerable difficulty in producing resistant strains *in vitro*. The nature of the disease, however, is such that one may anticipate the eventual development and spread of resistant strains. Even so, it is difficult to predict whether or not such a development will be of clinical and epidemiologic importance. That will depend upon whether or not the resistance will become a permanent characteristic of the strain and also whether that resistance will alter the human virulence of the strains. There is as yet no evidence on this point.

It must be borne in mind, however, that certain factors operative in some cases of gonorrhea militate against complete success, except where treatment is undertaken early. Gonorrhea is noted for its tendency to produce localized infections and to form pockets of pus, particularly in females. Sulfonamide drugs have failed in such cases because the purulent exudates

ures are encountered with doses of 300,000 to 500,000 units given orally than with 100,000 units given intramuscularly. Here again it is probably better to distribute the dose over a period of 12 hours or longer, and it may even be necessary to repeat the dose on successive days. The importance of starting the treatment on an empty stomach and of avoiding medication earlier than 1.5 to 2 hours, and preferably longer, after a meal should be kept in mind

In the treatment of complications of gonorrhea, one must differentiate between the cure of infection and the cure of the clinical disease.. Symptoms may persist for considerable periods after all evidences of active infection have subsided. As already noted, pelvic inflammatory disease in women may persist in spite of seemingly adequate therapy and apparent bacteriologic cure. Epididymitis may run its natural course under similar conditions. Gonococcic arthritis sometimes clears up rapidly with a brief course of penicillin, while in other cases, in spite of prolonged treatment, evidence of active infection persists until local instillation is used. Even under such conditions, however, pain, swelling, and sometimes limitation of motion may continue for some time after apparent bacteriologic cure.

Some observers have pointed out that treatment of acute gonorrhea with the usual doses does not prevent the development of syphilitic lesions in patients who may have acquired both infections simultaneously. This is true in spite of the fact that the gonorrheal infection may be completely cured. Furthermore, the dose necessary to cure the neisserian infection may not prevent the development of chancroid, or be sufficient to cure such infection if it is acquired at the same time

Treatment of Syphilis

In October, 1943, Mahoney, Arnold, and Harris made a brief preliminary report on the effect of penicillin in experimental syphilis in rabbits and on 4 cases of seropositive primary syphilis in man Their results and the further experimental studies of Mahoney, of Eagle, and of others held out considerable promise that a rapid cure of early syphilis had been discovered which was completely safe and lacked all the hazards of the arsenic and bismuth therapies Under the auspices of the Committee of Medical Research, a special penicillin panel was appointed to investigate all the various aspects of the treatment of early and late syphilis The preliminary results of the treatment during the first year were reported in September, 1944

At that time it had already been determined that penicillin has a profound and immediate effect in early syphilis, as indicated by the disappearance of surface organisms from open lesions, the healing of such syphilitic lesions,

interesting deductions from an analysis of the reported results. In the initial treatment of acute gonorrhea by a single course of intramuscular injection of penicillin, the number of failures decrease from over 30 per cent to between 3 and 5 per cent as the total dose increases from below 50,000 units to 200,000 units or more. For any given total dose, however, the percentage of failures seems to decrease progressively as the time between the first and the last dose is increased. The largest percentage of failures occurred when the total dose was given as a single injection, the least failures when the dose was divided and given at 2 to 3 hour intervals for 12 to 24 hours or longer.

The inadequacy of a uniform dosage schedule in the treatment of gonorrhea has already been pointed out by some observers It is probably best to decide on a dosage scheme which is usually adequate and most convenient for the particular physician or clinic and to observe at the end of that course the effect on the exudate and on the organisms in the smears or cultures. One soon learns to judge the type of response which is adequate. It usually means complete subsidence of symptoms and discharge, and negative cultures. In patients showing less than the optimum response to a single course at the first observation, preferably on the morning after the treatment, it had best be repeated with the same or, better yet, with an appreciably larger dose It should be pointed out, however, that while most recurrences will occur during the first week after treatment, there are some cases in which discharge and symptoms reappear only 2 or 3 weeks later.

Judging from the results of re-treatment of cases failing to respond to the initial course of therapy, some degree of resistance might possibly have been present or have developed in certain cases The percentage of failures with the larger doses used in the second course of treatment seems to be considerably greater than the percentage of original failures.

The results of treatment with penicillin in beeswax and oil, generally speaking, have not been as good as those obtained from multiple injections of the usual solutions of penicillin in saline given over an interval of 12 hours or more More than 10 per cent of failures have occurred in patients treated with a single injection of 50,000 to 100,000 units of penicillin in beeswax and oil; a similar large proportion of failures has also been noted after a single injection of 200,000 units Because of the variable absorption of penicillin when given in oil, it may be preferable, when using such preparations, to give 2 doses of 100,000 units 12 hours apart or even 3 doses at 8 hour intervals.

There are only a few published reports on oral ingestion of penicillin in the treatment of gonorrhea. Occasionally, patients have shown complete clinical cure with as little as 100,000 units In general, however, more fail-

Herxheimer's reaction occurred within the first 24 hours after penicillin treatment of early syphilis in almost 60 per cent of the cases. This usually consisted of fever alone, but in some instances there was an exacerbation of secondary skin lesions, with or without fever. Alarming reactions have been very few and have not interfered with subsequent treatment. It has been suggested that the treatment during the first day or two could well be carried out with half the dosage usually recommended and the treatment continued for an extra day or two This may reduce somewhat the incidence of Herxheimer's reactions Penicillin is apparently completely effective in early syphilis which is resistant to arsenic and bismuth therapy.

It also appears to be of great value in the prevention of congenital syphilis in infants born of recently infected mothers, and to have very favorable effects in early neurosyphilis, both the asymptomatic and meningeal types. In both types, the spinal fluid shows improvement with even greater rapidity than the blood serologic test It seems to be equally useful in infantile congenital syphilis and in the acquired disease. In infants, the total dosage used was from 20,000 to 60,000 units per kilogram of body weight, given over a period of 8 to 12 days Patients who have relapsed clinically or serologically after any dose of penicillin have been re-treated with doses of 1,200,000 to 2,400,000 units Until recently, no examples of penicillin resistance have been encountered Relapses of lesions apparently respond as promptly as do the initial ones It is at present expected, however, that the relapse rate in re-treated patients will be higher than in patients treated for the original attack, as is the case in chemotherapy with heavy metals

The 1944 report also included the results of treatment in 182 cases of late syphilis Most of them were cases of neurosyphilis, but cases of benign gummatous syphilis, ocular, and other forms of syphilis, and late congenital syphilis had also been observed for a comparatively short period. It was shown that the lesions of benign gummatous syphilis of skin and bones healed very rapidly, even with doses of 300,000 units given in 12 to 46 days. Visible healing of such lesions occurred with even greater rapidity than after treatment with heavy metals In interstitial keratitis of congenital syphilis the results were less spectacular, but half of the patients treated showed improvement Initial Herxheimer-like reactions were observed in about 20 per cent of the cases

The effect of penicillin on the blood serologic reactions in neurosyphilis was very clear and its effect on abnormal spinal fluid was even greater The greatest improvement occurred in the fluids showing the greatest abnormality, and apparently this improvement continues for at least 4 months after an 8 day course Larger doses give better results than the smaller

and a trend toward reversal of serologic findings. The immediate effects were found to be identical within a dosage range of 60,000 to 1,200,000 units, administered intramuscularly in 60 injections at 3 hour intervals, given day and night, over a period of 7.5 days The same immediate effects were obtained within a dosage range of 300,000 to 1,200,000 units given in a total of 30 injections in 4 days. These immediate effects, therefore, cannot be utilized to determine the optimum time-dose relationship. In man, one must depend on the incidence of relapse for this purpose.

When penicillin was administered alone, the incidence of relapse was found to bear a direct relationship to the total dose given intramuscularly over a period of 7 5 days. Relapses were more frequent on comparable dosages given intravenously than after intramuscular administration In some animal studies and in small groups of patients, the results suggested that penicillin in combination with mapharsen may be more effective than when either drug is given alone. The latter drug was given in doses of 5 to 6 milligrams per kilogram of body weight within 8 days.

At that time it was thought that the minimum dose, especially in secondary syphilis, should be not less than 1,200,000 units and that it probably should be more Subsequent observations suggested that relapses were less frequent when 2,400,000 units were given in 7.5 days than when half that dose was used. It has also been shown that the same number of units of penicillin seemed to be less effective when given in 30 injections in 4 days than when a similar dose was given in 60 injections in 7 5 days. The optimum interval between injections is still being studied, but it is now well established that an interval of 12 hours is unsatisfactory when the soluble preparations are given intramuscularly.

The results in early syphilis collected by the Committee on Medical Research and the United States Public Health Service up to August 1, 1945, have recently been reported The cumulative percentage of failures varied from 15 per cent on a dose of 2,400,000 units to 62 per cent after 600,000 units Failures after any given amount were twice as frequent when penicillin was given alone as when it was combined with arsenoxide and the percentage of those becoming seronegative after 7 months was greater among the latter Failure rates were higher for longer durations of disease than for shorter durations About 85 per cent of the failures were considered to be relapses and 15 per cent were possible reinfections The results in individual clinics varied markedly The change in the character of commercial penicillin which occurred during this time was reflected in the results of treatment of early syphilis; they were less satisfactory after May, 1944, than prior to that date.

was natural that attempts should be made to determine the value of penicillin in other spirochetal infections. Variable results have been obtained in experimental infections, but most of them have shown that all of the spirochetes are susceptible to some extent. Some *in vitro* studies have also given variable results with the methods available, but here again evidence for an effective action on the spirochetes could not be demonstrated in each instance. Reports on the clinical use of penicillin in spirochetal infections other than syphilis are frequently based on small numbers of cases except for the recent results in Vincent's infection, for which condition most of the clinical reports have been favorable

Yaws. As reported from the Johns Hopkins Hospital, primary and secondary yaws have responded to treatment in essentially the same manner as syphilis With doses of 15,000 units given intramuscularly every 3 or 4 hours, the spirochetes usually disappear from dark field preparations of the exudate from local lesions 16 to 40 hours after the first dose. Healing begins even before that time and progresses rapidly. All lesions seem to heal within 3 weeks, and most of the ulcers clear within 1 week although the treatment is given for only 5 or 6 days The late results have not yet been reported. The clinical and serologic results in tertiary yaws appear to be at least as good as with arsphenamine

Relapsing Fever. The spirochetes of this disease have proved sensitive to penicillin *in vitro* and in experimental infections in mice and rabbits. Doses approximating the toxic amounts have been necessary to effect a cure in some of the animals, especially in the rat There are no clinical reports available at this time, but it would seem that unless relapsing fever in humans is more susceptible than the infection in animals, penicillin treatment would not be warranted except in arsenic-resistant cases, or perhaps as an adjunct to arsenic therapy.

Rat Bite Fever This may be due to a Spirillum or to a Streptobacillus Fortunately, both of these organisms have proved susceptible to pencillin. Several cases of rat bite fever due to Streptobacillus moniliformis have been reported which were considered as having responded favorably to penicillin therapy Treatment of a single case of the spirochetal infection has already been reported, though others are known to have been treated with favorable results.

Weil's Disease A suppressive effect on pathogenic varieties of Leptospira, including L. icterohaemorrhagiae and L. canicola, has been demonstrated *in vitro* and in highly susceptible animals. Large doses were needed in guinea pigs; in this host the development of the disease could be prevented, but it could not be cured by penicillin after the infection was es-

ones, and the best results were obtained when the larger dose was given in 2 courses, that is, when the length of treatment was increased. There was prompt improvement in the cell count and protein content, and sometimes in the complement fixation and colloidal tests as well. Some degree of immediate clinical improvement is apparent in most of the symptomatic cases of neurosyphilis. *A trend toward sero-reversal in the blood test is* evident in a higher proportion of cases of late syphilis than was previously possible with chemotherapy. It is probably not necessary to give penicillin intrathecally in cases of neurosyphilis, but no definite opinion can be expressed on this point until more data become available.

Penicillin alone has proved equal to or more effective than either malaria alone or routine chemotherapy. A single dose of 4,800,000 units in not less than 7.5 days round the clock, using penicillin sodium in saline intramuscularly seems to make the best start and in the majority of cases of neurosyphilis has been an adequate total therapy In dementia paralytica, doses of 2,000,000 to 10,000,000 units of penicillin alone produced some clinical improvement in 46 per cent of the cases Spinal fluid cell counts and total proteins promptly became normal, and the colloidal gold and Wassermann's tests improved gradually Penicillin combined with malaria resulted in improvement in 58 per cent of the cases and the improvement in the spinal fluid was even more complete than with penicillin alone. Severe and even fatal Herxheimer's reactions have occurred in some neurosyphilitics being treated with penicillin

Moore recently summarized the status of penicillin treatment of syphilis as follows. "As matters stand at present, penicillin is a new and powerful *addition to syphilis therapy. How best to use it, alone or in combination* with other forms of treatment, is as yet undetermined but is under organized nation-wide, government-sponsored study from which definitive results may be expected rapidly to emerge" Studies of the value of arsenicals, fever therapy, and malaria in conjunction with penicillin are in progress

Just what effect the recent appearance of highly purified preparations will have on the results of chemotherapy as reported during the first 12 to 18 months cannot be foretold. *It is not known whether the observations* of Dunham and Rake that much of the antispirochetal activity of penicillin resides in the impurities which are removed in the course of purification have any counterpart in human therapy If they do, a new line of attack must be considered for the most effective treatment of syphilis.

Treatment of Other Spirochetal Infections

After the demonstration of the clinical effects of penicillin in syphilis, it

stillation of sulfonamides has not been widely used, and when thus given has not increased appreciably the number of favorable results. The fact that penicillin is not inhibited by pus and tissue autolysates suggested that this drug might give better results As already mentioned, diffusion of penicillin into the pleural cavity takes place during its systemic administration, but the concentrations obtained in the pleural exudate are usually less than those found at the same time in the serum and these are usually inadequate to cure the infection

Most reports on penicillin treatment of pneumonia have indicated that empyema does not develop if it is treated early When an empyema does occur after treatment, there is usually reason to suspect that it may have been present before the treatment began Few instances are reported, however, of the cure of empyema by systemic therapy, once infected purulent fluid has accumulated Since penicillin injected intrapleurally diffuses out rather slowly and high concentrations can be maintained in the pleural fluid for 12 to 48 hours after the injection of an appropriate amount, this type of therapy is obviously indicated When intrapleural therapy is used, the need for systemic penicillin would depend upon whether or not underlying infections of the lung or other tissues are still present and active. Indeed, the fact that serum penicillin concentrations similar to those obtained after intramuscular injections can be maintained for several hours after an intrapleural instillation of 100,000 units or more suggests that intramuscular therapy under such conditions might be unnecessary.

During the past 2 years reports have appeared in the literature on over 300 cases of empyema which were treated with penicillin. These may be divided into 3 groups: (*1*) typical empyemas following acute pulmonary infections, (*2*) post-traumatic and postoperative empyemas; and (*3*) a small group of cases of putrid empyema.

The first of these groups is the largest, and the organisms most frequently encountered are pneumococcus, beta hemolytic streptococcus, staphylococcus, mixed infections, nonhemolytic streptococcus, and micro-aerophilic streptococcus, in the order named Many of the patients received sulfonamides in addition to the penicillin, and it is generally noted that the sulfonamides had no curative effect in these cases Indeed, some authors have suggested that the use of sulfonamides tends to increase the occurrence of atypical empyema pockets in nondependent locations and in the interlobar spaces and creates difficult diagnostic and therapeutic problems It is impossible to learn from the reports the exact number of cases in which systemic penicillin therapy was used to supplement intrapleural therapy

Details concerning penicillin therapy are not given in every case. How-

tablished. In mice and in hamsters penicillin has been found to be about as effective as immune serum Few cases have been reported in the literature. From the results in those cases and from personal observations in 2 cases, it can be said only that penicillin may have some beneficial effect in the treatment of Weil's disease, but the results are not very dramatic even when doses of 300,000 units a day are used

Vincent's Infection The reported results of treatment of fusospirochetal infection of the mouth have been highly favorable. The beneficial effects of penicillin were first noted in the course of systemic treatment of patients with other conditions These were quite striking and improvement was more rapid than with any previous treatment Subsequently, when local therapy was tried, the response was likewise favorable. Spirochetes disappear rapidly from the mouth lesions when penicillin is given parenterally in doses of 15,000 or 20,000 units every 3 hours Patients note subjective improvement within 6 hours of the first intramuscular injection, although the lesions show improvement more slowly and definite improvement usually requires about 24 hours After that time, the membrane usually clears, bleeding tendency stops, and the odor disappears It may require from 1 to 10 days for a complete disappearance of the ulcers and exudate, depending on the severity of the infection Gingivitis, which often accompanies Vincent's infection, also disappears rapidly Fever subsides and general improvement occurs within 24 hours Recurrences have not been noted

The topical application of penicillin solutions in concentrations of 500 or 1,000 units per cc 4 times a day, or in the form of sucking or chewing troches or agar pastilles, have all proved effective when used alone or in conjunction with parenteral therapy The effectiveness and the low toxicity of the oral preparations is such that the treatment can be successfully carried out in ambulatory patients

It should be emphasized that the dosage of penicillin and the methods used in the treatment of Vincent's infections may mask the development of early syphilis As was noted on page 393, the dose may be effective in eliminating the spirochetes of syphilis from the local lesion and produce local healing without effecting a cure If the possibility of syphilitic lesions of the mouth exists, the patient should be followed serologically for some time after the treatment is completed

Treatment of Empyema

It has been a common experience that although sulfonamide therapy reduces the incidence of empyema complicating pneumonia it alone cannot cure this complication, once it has become established. Intrapleural in-

The cases of putrid empyema are of special interest. These form a special type of empyema, with a different etiology, pathogenesis, and prognosis. Cases of this sort are usually classed as surgical emergencies and immediate and open drainage has been suggested as essential for the best results, and even as a life-saving measure. Apparently, penicillin has altered the picture in these cases, so that it is no longer necessary to operate immediately. In some cases, it has been possible to effect a cure with penicillin and aspiration alone. The response of the patient depends to a large measure on the etiology and underlying pulmonary pathology. Each case, therefore, constitutes an individual problem

Improvement in almost all the cases of putrid empyema treated with penicillin has been reported, sometimes most dramatic improvement. The foul odor of the fluid disappears promptly, as does the toxic appearance of the patient. Most of the 13 cases of putrid empyema treated with penicillin intrapleurally so far reported also were given systemic penicillin therapy. Several of them followed lung abscess, 2 followed chest wounds, and the rest were of varied pathogenesis All but one or two were definitely improved, and 4 were cured with penicillin and aspiration alone. Only one developed abscesses of the chest wall at the site of aspiration, formerly a very frequent and very serious complication Operations were carried out in most of the cases in order to obliterate the cavity. It is of interest that 3 patients who were cured by treatment with aspiration and systemic penicillin injection alone had a bronchopleural fistula. There were 2 deaths, both in the operative group In one of them a massive hemoptysis was found at autopsy to have come from a lung abscess and the empyema was found to be obliterated

From the results reported in the literature thus far, as well as from our own experience, one cannot avoid the impression that postpneumonic empyema in the vast majority of cases can be treated successfully by repeated aspiration and intrapleural injections of penicillin without resort to operation. Localized infections, such as may occur in staphylococcic empyemas, may interfere with the complete success of this form of therapy. Early treatment is, of course, more likely to succeeed than treatment delayed until the exudate has become thick and the walls of the cavity covered with a thick layer of fibrin so that it is difficult to collapse The impression gained from many of the reports is that surgeons have been too impatient and have operated on patients who were showing a favorable response and might otherwise have been completely cured without surgical intervention These surgeons emphasize the long course of some of the cases that improved on the medical regime. Not enough stress is placed on the prolonged postop-

ever, the number of intrapleural injections varied from 2 to more than 15, with over half of the cases receiving 5 injections or less. The amount of drug given in the individual injections varied from 10,000 to 100,000 units, with most of the cases receiving between 25,000 and 60,000 units. Recent reports indicate that as much as 200,000 units in a single injection can be given intrapleurally without untoward effects. With such doses concentrations are maintained for 24 hours or longer in the serum and, in addition, high levels are present in the pleural fluid for as long as 48 hours Duration of therapy has varied from less than 1 week to almost 3 months. The great majority, however, were treated for less than 3 weeks One-third of the cases did not receive intramuscular therapy.

In this group of postpneumonic empyemas, 53 per cent were apparently cured without resort to surgical drainage, and a small number of cases were cured by systemic penicillin alone Some authors have reported cures with parenteral and intrapleural penicillin alone in over 90 per cent of cases of pneumococcic empyema. Others, however, have resorted to surgical drainage after or during penicillin therapy in more than half of their cases. Drainage was usually established by rib resection In most instances the operations were done when only a short trial of aspirations and intrapleural injections had failed, i e , either the pleural fluids did not become sterile or the fluid continued to accumulate. Only a small number of operations were done in order to collapse chronic cavities, although repeatedly negative cultures were obtained from the fluid

All observers agreed that the administration of penicillin was followed by a striking reduction in the toxemia and improvement in the general condition of the patient The mortality in the entire group was 4 per cent, including those who had come to operation It is generally agreed that the great disadvantage of treating empyema without surgery is the danger of the development of chronic empyema cavity. Less than 5 per cent of the cases were definitely classed as having become chronic, although this figure may be small because of inadequate follow-up.

In the group of posttraumatic cases, the data are rather scant. A significant number were cured by penicillin alone, without surgery, but most of them were treated by rib resection and some of these died. There were 4 deaths in a group of 14 cases of empyema which developed following chest surgery. In this group, as in the previous ones, it is difficult to determine how many of the cases might have been cured without resort to surgery. The etiology in most of these posttraumatic or postoperative cases is not stated, but some cases due to pneumococcus, streptococcus, and mixed infections have been reported

extensive areas of necrotic bronchopulmonary tissue. Inhalation is given regularly at 3 or 4 hour intervals day and night until the evidence of active infection subsides, and can then be given at 4 hour intervals during the day only. Later, the number of doses can be reduced to 2 or 3 daily. The individual inhalation dose may be from 25,000 to 50,000 units dissolved in 1 cc of saline and aerosolized by means of a jet of oxygen. Even greater concentrations of the more refined preparations have been possible without irritation, but a dose of more than 100,000 units per cubic centimeter is not well tolerated

Postural drainage and bronchoscopic aspiration are important adjuncts in the treatment of chronic pulmonary suppuration and are not obviated by the use of penicillin At the time of bronchoscopic aspiration penicillin may be instilled directly into the site of the lesion in dosages of 10,000 to 50,000 units in 1 to 2 cc of solution after each aspiration. In the hands of a skillful operator, good results should follow frequent bronchoscopic treatments given in this manner. Penicillin may also be incorporated with iodized oil in making bronchograms, which does not, however, remove the objections to the therapeutic use of iodized oils or any other forms of oils in the lungs.

In the preparation of patients for lobectomy, penicillin has proved of considerable value in improving the general condition of the patient and in reducing the incidence and severity of postoperative infections It has proved useful in lobectomies and pneumonectomies, whether for cancer or for severe and localized bronchiectasis or resistant lung abscesses. Treatment for 3 to 7 days before the operation with doses of 300,000 units a day is advocated Preoperative inhalational treatment, either alone or in conjunction with parenteral therapy, may prove even more effective. The treatment is continued for several days after operation or as long as there is danger of infection Postoperative empyema is less frequent after such preoperative preparation When fluid accumulates postoperatively and requires aspiration, it may be helpful to instill penicillin after each aspiration, the amount depending on the volume of fluid aspirated and on its character Small amounts are sufficient where thin, sterile fluid is obtained, while large amounts are best if there is a considerable amount of thick purulent exudate containing many bacteria

Penicillin has also been advocated in the treatment of severe asthma associated with chronic sinusitis and bronchitis In intractable asthma accompanying acute respiratory infections, treatment with sulfonamides in the past frequently rendered these cases more responsive to the usual therapeutic measures Penicillin is probably more effective in such conditions

erative course of patients subjected to rib resection with the long-continued draining sinuses which too frequently become chronic and almost universally become secondarily infected. The ugly scars and the local persistence of pain is also an important factor to consider. In a number of patients subjected to operation, the cavity has been found entirely obliterated after penicillin therapy. The fact that the pleural wall is thick with fibrinous exudate has not been shown to be of any serious consequence under these conditions. It is therefore suggested that medical treatment be continued for as long as 2 to 4 weeks, or even longer if necessary, unless large amounts of fluid continue to accumulate or there is evidence that the infection persists in spite of adequate and prolonged therapy.

As pointed out in the following section, penicillin has been highly successful in the prevention of empyema following operations on the lungs or thoracic cage

Treatment of Nontuberculous Suppurative Lung Disease

In patients with bronchiectasis and abscess formation resulting from staphylococcic or hemolytic streptococcic pneumonia, penicillin may be of great benefit and bring about considerable improvement or even a cure. In the first published report of such cases by Blake and Craige, the dose used would now be considered inadequate With larger doses, the results are sometimes striking Beneficial and highly gratifying results can also be obtained in many cases in which there is a more chronic type of pulmonary suppuration, with a mixed flora including fusospirochetes and anaerobic organisms.

When given systemically in doses of 200,000 to 300,000 units a day, patients with chronic nontuberculous pulmonary suppuration who are acutely ill, toxic, and febrile, and raise large amounts of foul sputum, frequently manifest rapid clinical improvement. The toxemia clears quickly, but the fever subsides more slowly. Chills and sweating no longer occur. The volume of sputum tends to decline after a few days and the odor disappears more rapidly. It is important to maintain treatment in full doses for longer periods than those usually recommended. A minimum of 2 to 3 weeks is necessary to bring about any lasting effects, and longer periods of treatment, up to 6 to 8 weeks or more, may be necessary to achieve the optimum results. The underlying process is not removed, however, and necrosis can be expected.

Treatment by inhalation alone or in conjunction with parenteral therapy may give better and even striking results. Both treatments or either one should be continued for long periods in order to permit healing of the

parts. It is best used parenterally for cases of established infection. It is also useful in reparative surgery in complicated wounds between the initial and definite surgery and treatment is maintained in such cases until the likelihood of infection has passed.

Penicillin has effectively controlled the great majority of cases in which staphylococci and hemolytic streptococci predominate. Bacillus pyocyaneus is not inhibited but, although it constitutes a nuisance, it really does little more than delay wound healing Proteolytic bacteria of putrid wounds are frequent in chronic wound infections. Anaerobic cellulitis is favorably influenced by systemic treatment with penicillin in large doses When locally applied, high concentrations of penicillin are necessary for the maximal inhibition of the proteolytic clostridia and the nonhemolytic streptococci. The proteus organisms and fecalis groups of streptococci are not influenced Putrid wound infection is usually considered to be a contraindication to extensive surgical revision or primary wound closure even if penicillin is given. The importance of general therapy with whole blood, plasma, and proper diet cannot be overemphasized Penicillin establishes with dramatic rapidity a positive nitrogen balance in patients chronically debilitated as a result of wound infections.

The list of susceptible organisms shown in Table I includes most of the pathogenic clostridia involved in clinical cases of gas gangrene. The results of treatment with penicillin have been more impressive than those previously reported from the use of sulfonamides, but they are still far from brilliant. Since the clostridia usually flourish in the presence of dead and devitalized tissue, the success of treatment will, of course, depend upon the skill and thoroughness with which surgical procedures are undertaken.

The value of penicillin in the treatment of gas gangrene has been demonstrated experimentally, and some favorable clinical reports have appeared in the literature Lyons stresses the necessity of the local treatment The largest single reported group of cases is that of Langley and Winklestein, who have recorded their experience with cases treated in an evacuation hospital. They re-emphasized the importance in the development of gas gangrene of the interval between the time the initial wound was received and the time of primary first aid dressing, as well as the delay in accomplishing definitive surgery Radical, extensive, thorough, and early surgery was found to be the most important factor in the prophylaxis and treatment of gas gangrene; sulfonamides, both locally and by mouth, had little or no effect. Penicillin in large doses was found to be an excellent adjunct in the therapy of established gas gangrene Insufficient in itself to control the infection, it was of inestimable value in conjunction with surgery and anti-

Where either acute or chronic infections with susceptible organisms are present, treatment by inhalation of penicillin aerosol may also prove effective. Caution, however, must be used in beginning treatment in such cases, lest the patient prove sensitive to penicillin. Such caution should be exercised during the first course of treatment and also when treatment is resumed after a long interval.

Treatment of Wounds and Gas Gangrene

The various uses of penicillin in surgery will not be treated in any great detail here. Meleney has pointed out the great difficulties in attempting to assess the effects of chemotherapeutic agents in the prevention of infection and in the treatment of various kinds of septic or potentially septic wounds. In established infections, the results in general have depended on the susceptibility of the infecting organism and on the character and location of the wound.

Most of the important features of penicillin therapy in the treatment of surgical infections were pointed out by Lyons. Both local and systemic therapy are useful, the latter to initiate treatment in all cases and to keep the infections localized. Supplemental topical application has proved effective in appropriate wounds and could be continued after systemic therapy or after operation. In his report, Lyons particularly emphasized the usefulness of penicillin in the immediate management of septic gunshot wounds and fractures. When susceptible bacteria predominate in the wound, there is prompt improvement during the treatment, with later recurrences. These recurrences are due to sequestrums of foreign bodies and the inability to sterilize such foci. Surgical intervention is necessary in most instances.

Churchill, in reviewing the surgical management of war wounds, has pointed out very clearly that sulfonamides and penicillin are not substitutes for good surgical management, particularly for the surgical excision of dead and devitalized tissue. Chemotherapeutic agents cannot sterilize dead and avascular tissue, nor do they prevent the septic decomposition of contaminated blood clots. On the other hand, penicillin and the sulfonamides have opened new and startling possibilities in wound management. The best use of penicillin is to extend the scope of surgery, permitting the achievement of a perfection in results not previously considered possible. The topical use of sulfonamides seems to contribute much to the favorable results of reparative wound surgery, and penicillin therapy is probably entirely unnecessary as an adjunct to the usual reparative surgery of soft

awaiting the necessary surgical procedures. The dose could be decreased after the activity of the infection has subsided.

Treatment of Skin Diseases

As might be expected, penicillin produces favorable results in infections of the skin in which sensitive organisms play a role either as causative agents or as secondary invaders Erysipelas has already been mentioned and responds rapidly, as do other streptococcic infections. The same is true of furunculosis and carbuncles, in which staphylococcus is the causative agent.

The course of *eczema* and *seborrheic dermatitis* is often prolonged and aggravated by secondary invaders, among which staphylococci and streptococci are the most common Local applications of penicillin once or twice a day in the form of wet dressings or as ointments, preferably the latter, have led to definite improvement. The treatment must usually be carried out for 1 to 3 weeks. Local application in sensitive patients must be carefully avoided, and it must be borne in mind that the patient may be sensitive either to the penicillin itself, to impurities in the preparation (other products of Penicillium or of the medium), or to the vehicle.

In the treatment of *impetigo*, penicillin applied locally in the form of paste, jelly, or ointment has proved very successful The crust should be removed thoroughly before each application and it should be applied once or twice daily for 1 to 2 weeks. The response to treatment seems to be more rapid than with other forms of therapy, including the sulfonamides. The organisms recovered from these cases are usually streptococci and staphylococci

Another dermatologic entity in which the same organisms are involved and which seems to respond favorably to penicillin is *sycosis vulgaris* (sycosis barbae) The treatment is essentially the same as for impetigo Shaving is discontinued during the period of treatment. In this condition there seems to be a tendency to relapse following local therapy

For deeper infections of the skin associated with fever, cellulitis, necrosis of tissues, or where there is lymphangitis or regional adenitis—indeed, in any very severe case—it is best to combine systemic therapy with local applications of penicillin In the purely superficial infections, however, the local application alone is usually adequate

ary infections. Variable results have been reported in cutaneous *actinomy-*

toxin. In the local therapy, application of penicillin by dusting it into the wounds was found to decrease the length and severity of the postoperative course. When it was used locally, it was mixed with sulfanilamide before being placed in the wound, between 30,000 and 100,000 units being used. Gas gangrene antitoxin in the experience of these workers appeared to have little preoperative value. Its main value was in neutralizing the postoperative toxemia; on the organisms themselves it had little effect. A minimum of 18 therapeutic doses was recommended when there was no serum sensitivity or other contraindications.

A small, but well-studied group of cases was reported by Gledhill from the British Army in Italy. Among 33 cases of gas gangrene, 11 had been previously treated by local application of calcium penicillin and sulfathiazole powder at the time of the primary operation; 2 had local instillation of 35,000 units of penicillin solution; 10 had parenteral courses of 100,000 to 450,000 units. Nevertheless, all of these cases developed gas gangrene—5 of them were among the severest cases. There was only one death among these 33 cases. It would, therefore, seem that penicillin had little value in prophylaxis when given in these various ways. The persistence of clostridia in some of the cases after recovery from the toxemia suggests that the *in vitro* action of penicillin differs from its action *in vivo*. However, penicillin given in large doses parenterally and locally did produce dramatic improvements in the general condition of the patients and this improvement occurred more rapidly than with any other form of treatment previously used. It was considered probable that the continued intensive treatment was responsible for the good results, but that early and efficient surgery remains the most important factor in prophylaxis and treatment of clostridial infections.

The divergence in the official attitudes of the Medical Departments of the British and American Armies with respect to the use of antitoxin is worth noting. The British have recommended it and consider it an essential feature both in prophylaxis and in therapy. The recommendations of the U. S. Army Medical Department have indicated that it is not of value in either, and have not recommended its use as a supplement to penicillin and sulfonamides.

In order to be effective in serious gas gangrene infection, penicillin must be used in fairly large doses, even if it is used only prophylactically. In potentially infected wounds, daily amounts of 200,000 to 300,000 units given in 2 to 4 hourly doses should be used, and even larger amounts are preferable if the presence of gas gangrene is suspected or diagnosed. A dose of 50,000 units every 3 hours would not be considered excessive while

equally effective for pneumococcic and streptococcic infections, but in infections with a diplobacillus or with other gram-negative organisms, the sulfonamides may be more effective than penicillin.

Penicillin treatment has been used successfully in chronic infections of the lids, conjunctiva, and cornea caused by staphylococci, streptococci, pneumococci, gonococci, and meningococci It is also indicated in the treatment of corneal ulcers resulting from trauma It seems to be inactive when used locally or systemically in the treatment of deep intra-ocular infections, such as iridocyclitis, choroiditis, and retinitis. The results in chronic membranous conjunctivitis caused by streptococci have been disappointing, reinfection occurring even after apparent recovery. Penicillin has been found useful in preventing infections following all types of trauma and operations on the eye

Treatment of Ear Diseases

It is interesting to note that the first American report on the clinical use of penicillin emanated from the Department of Otolaryngology at the Johns Hopkins Hospital. Crude penicillin prepared there by Fisher was employed in the local treatment of acute otitis media, acute and chronic mastoiditis, and acute and chronic sinusitis with better results than had previously been obtained with any other form of treatment. Used in this manner, penicillin was found to be nontoxic, noninjurious to tissues, and did not interfere with wound healing. It seemed to inhibit or entirely to eliminate the growth of most strains of staphylococci, streptococci, pneumococci, but it had no effect on gram-negative organisms

Shortly thereafter, the Floreys reported on the use of penicillin locally after mastoidectomy, with healing in such cases occurring very rapidly. Penicillin has been found most effective in the control of infections of the mastoid and contiguous structures, provided that the infections are caused by sensitive organisms. The blood stream can be rendered sterile and the spread of infection controlled by systemic administration, but many aural surgeons deem surgical intervention necessary to effect a cure. There are a number of reports, however, which indicate that operations can often be avoided in acute mastoiditis by prolonged and adequate treatment with penicillin One observer alone has reported cures by intramuscular penicillin without resort to surgery in 27 cases of scarlet fever mastoiditis. The same observer has also had remarkable success in treating acute otitis media, particularly when it occurs as a complication of scarlet fever.

The usefulness of penicillin as an adjunct to surgery has already been noted. Healing usually occurs very rapidly if penicillin is instilled directly

cosis, and in cases of *lymphogranuloma venereum*. Here again, the variable results may be attributable to the effect of penicillin on more susceptible secondary invaders Penicillin has proved to be ineffective in the treatment of acne vulgaris, psoriasis, granuloma inguinale, dermatitis herpetiformis, dermatitis repens, cutaneous leishmaniasis, cutaneous coccidioidomycosis, and other fungal infections of the skin including the trichophyton infections There is at least one reported case of chickenpox which developed while the patient was under systemic treatment with penicillin.

Treatment of Eye Diseases

Small amounts of penicillin probably enter most of the ocular structures after large systemic doses, none enters the lens, and none of the ocular tissues and fluids contain more than a trace of penicillin 3 hours after a single large injection. In animals and humans, topical applications of penicillin are more suitable for external infections of the eyeball and its adnexa than parenteral injections, but the latter, though not too effective, are more suitable for infections of the uveal and retinal layers. The highest concentrations of penicillin tolerated by subconjunctival injection is 25,000 units in 0.25 cc. of isotonic saline solution In the human eye, 10,000 units per cc. produces only slight smarting No pain or discomfort results from repeated instillation of penicillin solution, or corneal baths every hour with solutions containing 500 units per cubic centimeter

The solutions and ointments usually employed in ophthalmology contain between 200 and 2,500 units per cc. of solution or per gram of ointment. Subconjunctival injections and injections into the anterior chamber produce detectable amounts in the normal vitreous Penetration in the infected eye and after iridectomy is better than in the normal eye. Subconjunctival infections of the vitreous with a sensitive strain of staphylococcus have been successfully treated with penicillin instilled directly into the vitreous, or by subconjunctival injections or injections into the anterior chamber, but not by intravenous injection. Ionization increased the penetration of penicillin into the aqueous The concentrations obtainable by iontophoresis are about tenfold those obtained with a corneal bath, according to some authors, but this has been disputed by others who have shown that penicillin is not readily ionized

Burns of the eye, because of their proximity to the mouth and nose, frequently become infected with staphylococci or streptococci Such burns heal more rapidly when a penicillin ointment or jelly is used than with sulfonamides Penicillin has been found effective in cases of staphylococcic infections which resist sulfonamide therapy. It is apparently

ant. In experimental infections in mice, penicillin will prevent otherwise lethal infection, provided that the infecting dose is not excessive and that the interval between infection and treatment is not too long

In 3 cases in man, definite and rapid clinical improvement followed treatment with 150,000 units per day. The causative organism could no longer be found in smears of the lesion after 1 to 3 days on this dose. In view of the fact that some strains require much higher concentrations than staphylococcus *in vitro*, it is probably best to use doses of 300,000 units a day until the general condition of the patient improves, the smears become negative, and the local lesion shows definite signs of healing. Treatment should probably be continued with smaller doses until the lesion is entirely healed.

Another series of 25 cases of cutaneous anthrax has been reported B. anthracis was isolated from blood cultures of 3 of these cases before treatment. Total doses of 1,000,000 to 4,000,000 or more units of penicillin were used Sulfadiazine was used in only 3 cases and antiserum was not given to any B. anthracis could no longer be isolated from the blood after 24 hours or more of treatment All lesions showed continued progression after treatment had been begun, but viable anthrax organisms were recovered from the lesions of only 3 cases after 24 hours of treatment All of the patients recovered uneventfully

Diphtheria. The diphtheria bacillus is susceptible to penicillin *in vitro*, but some strains may require extremely high concentrations Since the actual site of infection is usually quite superficial, it might prove susceptible to topical therapy, particularly in the case of wound infections The diphtheria carrier state may be temporarily suppressed during intramuscular treatment, but positive cultures are usually obtained after treatment is stopped In established infection, the need for antitoxin is not obviated since the penicillin cannot be expected to neutralize the toxin. All types of local therapy, including swabbing, spraying, the use of sucking or chewing troches, and aerosol administration suggest themselves as adjuncts to antitoxic therapy in diphtheria, but reports on results are not available for analysis

Ludwig's Angina This is a very serious type of spreading infection of the floor of the mouth associated with marked swelling of the structures. It is frequently fatal, and death usually is due to respiratory obstruction. Tracheotomy must be resorted to in most cases in order to relieve the obstruction The hemolytic streptococcus is probably the most frequent organism involved, but pneumococci, staphylococci, Vincent's spirochetes, micro-aerophilic streptococci, and various anaerobes have been reported

into the mastoid cavity. As a rule, the ear becomes dry by the fifth postoperative day, and convalescence is considerably shortened by this treatment. The drug may be introduced through a ureteral catheter left in the wound at the time of operation. Penicillin seems to be more effective than the sulfonamides in all cases in which penicillin-susceptible organisms are involved. Beneficial results from general therapy with penicillin have also been reported in cases of chronic otitis media, in labyrinthitis, cerebral abscess, epidural abscess, lateral sinus thrombosis, petrositis, and otitic meningitis Most of the reported cases had failed to respond to sulfonamide drugs but had yielded to adequate local and systemic penicillin therapy. The results in acute sinusitis treated by local irrigations have not been satisfactory. Better results in this condition are claimed for aerosol penicillin given by a special technic.

Treatment of Miscellaneous Conditions

It is not necessary to consider in any detail all of the other infections in which penicillin has been used with varying success [illegible] gree of success which can be anti[illegible] predicted [illegible] and the r[illegible] As already indicated, the [illegible] favorably to penicillin are those in which the [illegible]ing organisms are susceptible, are completely accessible to readily maintained concentrations of the drug, and in which substances able to inhibit penicillin action or organisms producing such inhibiting substances are not present at the site of infection In localized infections in which the organisms are inaccessible to systemic therapy but can be reached by topical injections, the success will usually depend on the extent to which the organism and drug can be brought together Strictly localized or superficial infections might be expected to respond to topical application even when the organisms are not highly susceptible The diseases already discussed have served to illustrate these general principles A few other specific infections and some types of infection concerning which some information is available may be mentioned briefly

Anthrax In the past, sulfonamides and specific antiserum have been used with considerable success in the treatment of anthrax There is general agreement that attempts to remove the lesion are fraught with great danger and are strictly contraindicated The causative organism is susceptible to penicillin *in vitro*, but strains apparently vary considerably in their sensitivity. Some strains have been reported as being as susceptible as staphylococci, while others have been more than 100 times more resist-

Ducrey bacillus. Others have used doses of 300,000 to 600,000 units over a period of 7 5 days and succeeded in healing most of the small chancroidal lesions, some larger ones requiring sulfonamide therapy after that time. In most cases, sulfonamides will probably be found to be more effective than penicillin and are probably to be preferred, except in patients who cannot tolerate them. In the latter, local sulfonamide therapy may be used advantageously to supplement systemic penicillin therapy, provided the patient is not also sensitive to local sulfonamide therapy.

Actinomycosis. Although the causative organism of this disease has been found to be fairly sensitive to penicillin, the clinical results have been quite variable and on the whole disappointing. Some improvement usually takes place in the patient's general condition and in the local lesions, and the infection has been arrested in certain cases of isolated and accesible lesions The nature and multiplicity of the lesions and the inaccessibility of many of the foci are probably responsible for the failures Treatment with penicillin should be prolonged and intensive, and may profitably be supplemented by or alternated with sulfonamide therapy when feasible. Surgical drainage of accessible suppurating areas and local instillation of penicillin should be helpful as an adjunct to systemic therapy.

Peritonitis and Puerperal Infections Several severe cases of puerperal infections are included in the clinical reports on the use of penicillin Cases in which hemolytic streptococci, staphylococci, and anaerobic streptococci were involved responded very favorably Many of these were treated after intensive sulfonamide therapy had failed Cases of primary peritonitis due to the hemolytic streptococcus or pneumococcus have responded favorably to sulfonamide therapy, and some cases have been reported in which penicillin has been used successfully Penicillin seems to diffuse into the peritoneal exudate somewhat better than into effusions of other serous cavities so that infections with susceptible organisms should be amenable to penicillin therapy, provided that treatment is given in large doses and started before the infection becomes walled off and before thick-walled abscesses have developed Topical application of penicillin combined with sulfonamides may be used at the time of abdominal operation in cases of potential or established infections Since resistant organisms of the colon group are frequently involved, the combined use of sulfonamides and penicillin systemically before and after operations is probably to be preferred Streptomycin may also be effective in such cases

Crile has recently presented a preliminary report on the systemic use of massive doses of penicillin in the treatment of peritonitis In 30 cases with established peritonitis, intra-abdominal inflammatory masses, or excessive

in these infections. Intensive sulfonamide therapy has sometimes been successful and surgery has been avoided by its early use. Two groups of cases have been reported in which systemic treatment of Ludwig's angina with penicillin has had highly favorable results. In some cases, convalescence was markedly shortened and in most cases, surgery became unnecessary under this treatment. Early and intensive therapy is essential to bring about such results. One must be prepared, however, to resort to tracheotomy in any case in which respiratory obstruction has developed.

Agranulocytic Angina. The exact etiology of agranulocytosis is not entirely clear. It is well established that the prolonged use of some of the most popular drugs employed in modern therapeutics may give rise to this condition. Aminopyrine, sulfonamides, and thiouracil are the most common offenders. The results of recent experimental studies suggest that various types of specific deficiencies play an important predisposing role. Severe infections are important factors both in the pathogenesis of this condition as well as in the frequently fatal complications. Because the disease, when untreated, has a high mortality, many forms of therapy, including blood transfusions, pentnucleotide, bone marrow preparations, liver extracts, pantothenic acid, and folic acid have been used simultaneously and successively. The sulfonamides have been employed successfully in some cases, particularly when associated with infections, but they have also been employed in cases in which similar drugs were presumably the responsible agents. The nature of the recovery process and the confused therapy makes it difficult to evaluate most of these reports.

It is natural that penicillin, because of its low toxicity and its effectiveness against many bacteria, should be used in cases of agranulocytic angina, especially in those resulting from sulfonamide therapy. Favorable results are reported but, as with the sulfonamides, they are difficult to evaluate. Removal of the causative agent is probably the most important feature in the treatment. The prevention and treatment of underlying or complicating infections, however, are probably also very important and this is most effectively accomplished by penicillin, when susceptible organisms are involved.

Chancroid. The results of *in vitro* tests for sensitivity of Ducrey's bacillus have given varying results. While some strains apparently are susceptible, others are quite resistant. The clinical results likewise have varied widely. Some observers have noted that chancroidal infections develop in spite of continued therapy with doses of 5,000 to 10,000 units of penicillin every 3 hours. They suggest that in some cases of syphilis treated with penicillin, resistant chancres may be due to a mixed infection with the

the evidence is not entirely convincing since a majority of these patients received sulfonamides during the most serious stage of their illness. It is possible, however, that some strains are susceptible to concentrations which might be obtained with large doses, particularly in patients who are on a low fluid intake or have cardiac or renal insufficiency. Some strains of Friedlander's bacillus have also been found to be more susceptible to penicillin X than to penicillin G It has also been noted earlier (page 382) that occasional meningeal strains of H influenzae are susceptible, and two such cases apparently responded favorably to parenteral and intrathecal penicillin therapy. However, such cases are difficult to evaluate, since sulfonamides have usually been given as adjuvants One case of empyema has been reported in which the causative organism was a gram-negative bacillus that was more sensitive to penicillin than to streptomycin. A cure was obtained by intrapleural penicillin alone, without resort to surgery.

Pulmonary and other forms of tuberculosis, and all types of leprosy are resistant to sulfonamide therapy, although temporary improvement is frequently noted in patients who are acutely ill and may have secondary bacterial infections. The same has been noted with penicillin.

The failure of acute rheumatic fever to respond favorably has already been noted This disease is not prevented even by early treatment of the antecedent pharyngitis Rheumatoid arthritis likewise has not been influenced in the least by penicillin therapy

There is no evidence whatever to suggest that penicillin is of any value in the treatment of any neoplastic disease in man except as it may produce clinical improvement in the general condition by its effect on secondary infections with susceptible bacteria.

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contamination of the peritoneal cavity from ruptured abscesses, treatment with 100,000 units of penicillin every 2 hours intramuscularly for 2 days and with diminishing doses for 6 more days resulted in marked improvement. None of the cases developed intraperitoneal abscesses or complications. A later report by the same author includes 50 cases with only 1 death.

Urinary Tract Infections. As might be expected from the fact that gram-negative bacilli and the fecalis group of streptococci are in general markedly resistant to penicillin, this drug has not been very successful in most cases of infections of the urinary tract Penicillin, however, is excreted in fairly high concentrations into the urine, and some strains of Str. faecalis and of proteus bacillus are susceptible to concentrations which are readily obtained in the urine. Urinary tract infections with such strains and, of course, the less frequent infections with hemolytic streptococci or staphylococci may be expected to respond to penicillin therapy to some extent. Failures, however, are frequent even in staphylococcic infection This may be due to the presence of mixed infections with resistant strains, particularly with colon bacilli which may actually inhibit penicillin action; the poor results may also be due to abscesses in the renal and perirenal tissues or to the presence of other complicating factors Recurrences are to be expected, even in cases in which there is temporary improvement Combined treatment with penicillin and sulfonamides, therefore, is to be preferred whenever that is feasible.

Conditions Not Favorably Affected by Penicillin Table II contains a long list of organisms and conditions in which there is evidence to indicate that no beneficial results may be expected even from prolonged treatment.

In rickettsial infections, there is experimental evidence to suggest that large concentrations might reduce the severity and the fatality of these diseases, but there is no clinical evidence in support of these experimental findings.

Thus far, there is no convincing evidence that any beneficial effects can be expected in any of the known virus diseases or in the primary atypical pneumonias of unknown etiology (virus pneumonias) except insofar as they are complicated by infections with susceptible bacteria The same can be said of infections caused by fungi, other than actinomycosis, by yeasts, protozoa, or by pleuropneumonia-like organisms

Infections with all forms of gram-negative bacilli have proved resistant The only exceptions are the chancroid infections, as already noted, and Friedlander's bacillus infections Occasional cases of Friedlander's bacillus pneumonia have been reported as responding favorably to penicillin, but

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Problem of the Rhesus Antigen in Medicine*

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The subject of the rhesus antigen is only five years old, yet it has already become so extensive and involved that only specialists can be expected to be fully acquainted with every ramification of the problem. This review summarizes the more important facts of this complicated subject, with particular reference to its clinical applications It is hoped that the review may serve as an adequate introduction to the problem, so that the reader will be able to read future articles in this field with proper perspective and with full understanding of the theoretic background and its practical implications.

The Standard Rh Factor

The rhesus, or Rh, factor got its name because the original work of Landsteiner and Wiener (1) was carried out with antisera prepared by injecting the blood of rhesus monkeys into rabbits (Later, it was found (2,3) that more satisfactory sera could be prepared by immunizing guinea pigs instead of rabbits) As was to be expected, antirhesus sera agglutinate the red blood cells of rhesus monkeys Landsteiner and Wiener found that certain antirhesus sera also contained a special agglutinin which clumped the red blood cells of approximately 85 per cent of the Caucasian race Evidently, the red cells of these individuals contained a special blood factor, different from any previously found, which was related to a certain fraction of the antigens in rhesus blood To indicate this, the newly discovered factor in human blood was designated as the Rh factor, and individuals whose red blood cells are clumped by antirhesus sera are said to be Rh positive, while those whose blood cells are not clumped by antirhesus sera are said to be Rh negative.

Most of the original work on the Rh factor was carried out with the aid

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TABLE I
INCIDENCE OF THE Rh FACTOR IN DIFFERENT PEOPLES

Population	Investigators	Number of subjects tested	Rh positive, per cent	Rh negative, per cent	Source of testing serum
Caucasians					
U.S.A.	Landsteiner and Wiener (2)	448	84.6	15 5	Guinea pig
U.S.A., mostly non-Jewish	Wiener and Sonn (13)	1,818	85 5	14 5	Human
U.S.A.; almost entirely Jewish	Wiener (14)	676	87 9	12 1	Human
U.S.A.	Levine (15)	1,035	86.6	13 4	Human
U.S.A.	Tisdall and Garland (16)	22,133	85.8	14.2	Human anti-Rh_0'
U.S.A.	Unger (17)	2,438	83.7	16 3	Human
U.S.A.	Fisk and Foord (4)	927	85 0	15 0	Guinea pig
England	Taylor and Race (18)	3,896	84 4	15 6	Human
Wales	Hoare (19)	1,122	84 6	15 4	Guinea pig
Sweden	Broman (19a)	937	86 6	13 4	Guinea pig and human
Germany	Dahr (20)	1,756	84 0	16 0	Guinea pig
Australia	Simmons et al (21)	3,641	82 3	17 7	Human
Honolulu	Pinkerton (22)	911	85 1	14 9	Human
Canada; Jewish	Lubinski et al (23)	514	91 4	8 6	Human
Canada, non-Jewish	Lubinski et al. (23)	325	84 6	15 4	Human
Negroes					
U.S.A.	Landsteiner and Wiener (2)	113	92 0	8 0	Guinea pig
U.S.A.	Wiener et al. (24)	223	89 2	10 8	Human
U.S.A.	Levine (15)	264	95 5	4 5	Human
U.S.A.	Tisdall (16)	283	90 1	9 9	Human
African Bantu	Lewis and Altman (25)	150	93 0	7 0	Human
American Indians					
U.S.A.	Landsteiner et al (26)	120	99 8	0 2	Guinea pig
Mexico	Wiener et al. (27)	98	100	0	Human
Asiatic Indians	Wiener et al (33)	156	90 3	9 7	Human
	das Gupta (34)	420	90	10	Rabbit
Chinese					
U.S.A.	Levine and Wong (28)	150	99 3	0 7	Human
U.S.A.	Wiener et al (29)	132	98 5	1 5	Human
Hawaii	Pinkerton (22)	127	100	0	Human
Japanese	Waller and Levine (30)	150	98 7	1 3	Human
	Miller and Taguchi (31)	180	99 4	0 6	Human
	Graydon and Simmons (32)	400	99 7	0.3	Human

TABLE I (*continued*)

INCIDENCE OF THE Rh FACTOR IN DIFFERENT PEOPLES

Population	Investigators	Number of subjects tested	Rh positive, per cent	Rh negative, per cent	Source of testing serum
Japanese	Pinkerton (22)	489	99 6	0.4	Human
Hawaiians	Pinkerton (22)	72	100	0	Human
Filipinos	Pinkerton (22)	51	100	0	Human
	Simmons *et al* (21)	382	99 7	0 3	Human
Fijians	Simmons *et al* (35)	200	100	0	Human
Maori (New Zealand)	Graydon and Simmons (36)	267	100	0	Human
Australian aborigines	Wilson *et al* (37)	381	99 8	0 2	Human
Papuans	Graydon and Simmons (36)	455	100	0	Human
Indonesians	Simmons *et al* (39)	396	99 0	1 0	Human
Porto Ricans	Torregrosa (40)	179	87 7	12 3	Human
Chileans	Vaccaro and Meza (41)	119	92 5	7 5	Human

of animal immune antirhesus serum, but more recently the tendency has been to use anti-Rh serum of human origin One reason for the preference for human anti-Rh serum is that the animal antirhesus sera cannot be used for classifying the blood of newborn infants, since such antirhesus sera strongly agglutinate the red blood cells from all fetuses and newborn infants whether Rh positive or Rh negative (4), thus indicating that in the neonatal period the red blood cells contain a special antigen which is absent later in life (5). This special antigen in neonatal blood is related to an antigen present in rhesus blood, but differs from that responsible for the reactions of the Rh test—perhaps another case of ontogeny recapitulating phylogeny. Another reason why human anti-Rh sera are preferred is that the best human antisera give stronger reactions than the best animal antirhesus sera, so that less experience is required to obtain satisfactory results with the human antisera Finally, the Rh blood types can be determined only with human antisera (page 453)

Since all animal immune antirhesus sera give identical reactions (2) they serve as a convenient standard On the other hand, three distinct varieties of anti-Rh agglutinins have been identified in human antisera (6), one of which (standard anti-Rh, or simply anti-Rh_o), gives reactions identical with the original antirhesus serum. The other two Rh agglutinins are designated as anti-rh′ (70 per cent positive) (7), and anti-rh″ (30 per cent positive) (8–10). The blood factors detected by the three human Rh

agglutinins are designated as Rh_o, rh′, and rh″, respectively. The clinical importance of the Rh factors depends on their antigenicity for individuals lacking them. Since Rh_o is far more antigenic than rh′ and rh″, almost all clinical problems caused by the Rh factors involve factor Rh_o. Ordinarily, therefore, when the terms "Rh positive," "Rh negative," "Rh factor," "anti-Rh agglutinin" are used without special qualification, it is the original rhesus factor or Rh_o factor that is referred to, and not rh′ or rh″ (11,12)

The distribution of the Rh factor is not the same in all populations (2); among white individuals, the highest frequency for the Rh-negative type has been encountered in Australia, the lowest among Canadian Jews and Asiatic Indians (Table I). Mongolian races (Japanese and Chinese), natives of southeastern Asia and the Pacific Islands, and American Indians are all characterized by the virtual absence of the Rh-negative type Negroes have an intermediate frequency of Rh-negative individuals.

As has been demonstrated by Landsteiner and Wiener (2), the Rh factor is inherited as a simple Mendelian dominant by a pair of allelic genes, *Rh* and *rh* Thus, Rh-negative individuals are always homozygous (genotype *rhrh*), while Rh-positive individuals may be homozygous (genotype *RhRh*) or heterozygous (genotype *Rhrh*). Therefore, when both parents are Rh negative, all the children must be Rh negative. If one parent is Rh positive and the other Rh negative, then either all the children will be Rh positive (when the Rh-positive parent is homozygous) or half of the children will be Rh positive and half Rh negat[illegible] parent is heterozygous) When both parents ar[illegible] will be Rh positive, except when both [illegible] case one-fourth of the children will be Rh negative Some of the published data on the heredity of the Rh factor are summarized in Table II;

TABLE II

HEREDITY OF THE Rh FACTOR*

Mating	Number of families	Children		
		Rh+	Rh−	Totals
Rh+ × Rh+	139	400	29	429
Rh+ × Rh−	41	85	27	112
Rh− × Rh−	9	0	37	37
Total	189	485	93	578

* Landsteiner and Wiener (2) · [illegible] rhesus serum Wiener and Sonn ([illegible] Rh_o serum. Dahr (20) · 89 familie[illegible]

it shows that the findings are in good agreement with what one would expect on the basis of Landsteiner and Wiener's theory.

Clinical Significance of the Rh Factor

Rh-negative individuals may become sensitized to the Rh factor, and such sensitivity may give rise to complications during blood transfusions (43) and in pregnancy (44). While the presence or absence of the Rh factor in the red cells is determined by heredity, Rh antibodies are acquired. At any rate, no convincing evidence has yet appeared of natural sensitivity to the Rh factor. Sensitivity may result after an Rh-negative individual has been exposed to the Rh factor

It should be emphasized that individuals differ markedly in their capacity to be sensitized, so that on the average only 1 in 25 to 50 Rh-negative individuals exposed to the Rh factor develop clinical evidence of Rh sensitization The ability to become sensitized is conditioned by heredity through a pair of allelic genes, K and k, where K confers the capacity to become sensitized while k is the contrasting normal gene (45). About 97 per cent of white individuals belong to genotype kk, and therefore resist sensitization, or, at least, are not readily sensitized About 3 per cent belong to genotype Kk; these are the individuals who usually develop clinical manifestations of Rh sensitization. The rare individuals who belong to genotype KK are presumably the easiest to sensitize

Rh-negative individuals may be exposed to the Rh factor and become subject to Rh sensitization in one of two ways. (*1*) as a result of a transfusion of Rh-positive blood, or (*2*) as a result of a pregnancy with an Rh-positive fetus If the Rh-negative individual is of the type capable of becoming sensitized (genotype Kk or KK), Rh antibodies will be produced following such exposure When a sensitized Rh-negative individual is given a transfusion of Rh-positive blood, a dangerous hemolytic reaction may result, even though the donor selected belongs to the same blood group as the patient Moreover, if the patient is a woman who subsequently bears an Rh-positive fetus, her Rh antibodies may pass through the placenta and combine with the red cells of the fetus, giving rise to one or another manifestation of congenital hemolytic disease (erythroblastosis foetalis).

Rh Factor in Blood Transfusion

Until a comparatively short time ago, it was generally believed that hemolytic transfusion reactions could not occur if patient and donor belonged to the same blood group During the decade 1930 to 1940, the widespread adoption of the citrate method of transfusion and the introduction

of blood banks caused a tremendous increase in the therapeutic use of blood, and the occasional occurrence of intragroup transfusion hemolysis became more noticeable. Sporadic reports began to appear of hemolytic reactions after *transfusions of blood of the correct blood group*, and several careful workers even reported that in such cases subsequent tests revealed that the patient's serum contained atypical iso-agglutinins capable of clumping the donor's red cells. Nevertheless, these reports were questioned in most quarters because of their rarity and because no attempt was made to correlate the cases with *one another.*

About this time Wiener and Peters (43) encountered 4 cases of intragroup transfusion hemolysis, 2 of them fatal. In 3 cases which were available for study they succeeded in demonstrating the presence in the patient's sera of irregular iso-agglutinins unrelated to the four blood groups. The 3 sera *gave identical reactions with one another and with the antirhesus immune* sera. Moreover, the 3 patients all proved to be Rh negative and the donors, whose blood had caused the hemolytic reactions, were all Rh positive. This proved that intragroup incompatibility with regard to the Rh factor was the cause of the reactions. When, within the short space of a year, 10 *similar cases were encountered* (7) *it became evident* that the Rh factor was the explanation for at least 90 per cent of the intragroup hemolytic transfusion reactions.

In individuals who become sensitized to the Rh factor and have intragroup hemolytic reactions, the history usually follows a stereotyped pattern. The mechanism can perhaps be understood more easily if we first consider the situation with regard to the A and B factors. The sera of normal adults contain the iso-agglutinins anti-A or anti-B, or both, which correspond to the agglutinogens absent from their red cells (*Landsteiner's* rule). Since the natural anti-A and anti-B iso-agglutinins are usually of low titer, an initial transfusion of incompatible blood may be followed by only a mild hemolytic reaction or by inapparent hemolysis lasting some hours or days. However, such a transfusion will stimulate the production of immune anti-A *and anti-B iso-antibodies, whose titer will usually reach* its peak within 10 to 20 days after the transfusion (46–48). In the presence of these high-titered immune iso-antibodies, a transfusion of incompatible blood may be expected to cause a violent and frequently fatal reaction (49). Furthermore, if the natural iso-agglutinins are of high titer, or if the *patient is a woman sensitized by a pregnancy with a child of an incompatible* group, even a first transfusion of incompatible blood may cause a severe or fatal hemolytic reaction.

A woman of group O giving birth to an infant of group *A may produce*

high-titered anti-A iso-agglutinins, while the titer of the anti-B iso-agglutinins would usually be unaffected in such a case (50). Other incompatible combinations may have a similar effect. Apparently, the rise in titer, when it occurs at all, takes place most frequently 1 to 2 weeks after delivery (51–53). This suggests that during labor and delivery, due to disturbances at the placental site, small quantities of fetal blood or secretions may gain access to the maternal circulation. It is evident that a mistake in blood grouping when selecting donors for blood transfusions is more apt to cause a serious reaction in women who have borne children than in male patients.

The same general principles apply in intragroup incompatibility as for A–B incompatibility, except that Rh-negative individuals have no natural antibodies for Rh-positive blood.* As a rule, a single transfusion of Rh-positive blood into an Rh-negative patient will not stimulate the prompt production of specific Rh iso-antibodies as in the case of the A–B factors; in fact, Rh-positive blood cells will survive and function just like Rh-negative blood in the circulation of nonsensitized Rh-negative individuals for as long as 3 to 4 months (43). Before a patient who can be sensitized to the Rh factor will respond, he or she must have a background of exposure to the antigen. For example, if an Rh-negative patient has had a transfusion of Rh-positive blood from 6 months to several years previously, or has had one or more pregnancies in the past, he or she may then be ready to respond to further exposure to the Rh antigen by producing Rh iso-antibodies. When such a patient is given a transfusion of Rh-positive blood, there will usually be no untoward reaction, but the red cells will be rapidly eliminated from the circulation, and within a week or two Rh antibodies will appear in the serum. Another transfusion of Rh-positive blood at this time will usually cause a serious hemolytic transfusion reaction (54).

These principles are illustrated by the following two case reports from the original paper of Wiener and Peters (43). They are cited with slight modifications, to conform with our present knowledge of the subject.

Case 1. In January, 1937 the patient had undergone operation for a perforated gastric ulcer, and received a postoperative blood transfusion. On November 22, 1939 he was admitted to the hospital for treatment of recurrent chills and fever. Three days later the patient, who belongs to group A, was given a transfusion of 200 cc. of fresh, citrated, group A blood. About an hour after the transfusion he had a chill that was slightly more severe than those on previous days, but there was no hemoglobinuria. The temperature dropped to a subnormal level and remained subnormal for a week. The patient was then given 2 transfusions, 250 cc. each, on November 27 and November 30, both from the same group A donor but

* Two exceptions to this statement have recently been encountered by the author

not the donor who gave the blood on November 22. The patient was discharged on December 7 but readmitted to the hospital 2 days later because of recurrence of chills, fever, headache. On December 12, he was given a transfusion of 200 cc. of blood from the donor who had given the transfusion on November 25 (18 days previously); 20 minutes later the patient presented the signs and symptoms of a severe hemolytic reaction. Hemoglobinemia and hemoglobinuria were present Urination ceased completely, and rather persistent and at times bloody vomiting ensued Bleeding and coagulation times were prolonged. Blood urea rose up to 250 mg. per 100 cc, creatinine to 14 mg. per 100 cc. Complete anuria lasted a week; on the eighth day the patient voided 50 cc. of urine, with a resumption of the anuria on the ninth day. So far the patient had been treated with intravenous glucose and diathermy On the tenth day, following splanchnic block, there was an immediate outpouring of urine; the blood urea dropped to 45 mg. per 100 cc, the creatinine to 1.9 mg. per 100 cc Thereafter the patient improved steadily.

Grouping tests confirmed the fact that the patient and donors all belonged to group A, while matching tests by the usual technic showed no incompatibility. However, the patient proved to be Rh negative while the donor whose blood had caused the hemolytic reaction was Rh positive, by a special technic Rh antibodies could be demonstrated in the patient's serum. Presumably, the donor who had been used in 1937 was also Rh positive, this transfusion provided the necessary background for Rh sensitization. While the transfusion of Rh-positive blood on November 25 caused no serious reaction, it provided the stimulus for the production of Rh iso-antibodies which caused the hemolytic reaction on December 12 when this donor was used again. Tests on the blood of the donor used for the transfusions on November 27 and 30 explained why no reactions had occurred—the donor proved to be Rh negative. By differential agglutination, the red cells of the Rh-negative donor were found to survive normally in the patient's circulation, in contrast to the Rh-positive blood which was promptly hemolyzed

Case 2. The patient, a 52 year old woman belonging to group O, received a transfusion of 500 cc of fresh citrated blood on the day following an abdominal operation Later the same day, a second transfusion of 300 cc was given; a third transfusion of 250 cc was given on the third day, a fourth transfusion of 500 cc on the eighth day, the fifth and last transfusion on the thirteenth day. Preliminary to each transfusion, the bloods of patient and donor were cross-matched, and all the transfusions were from different group O donors. There were no febrile reactions whatever to the first 4 transfusions However, during the week following

the third transfusion, it soon dropped back to 65 per cent and continued to fall after the fourth transfusion Within 15 minutes after the fifth and last transfusion, there was a severe chill lasting about half an hour, accompanied by a rise in temperature to 104 F. Hemoglobinemia appeared, followed by marked oliguria, and the patient became noticeably jaundiced The blood urea concentration rose to 163 mg per 100 cc., while the hemoglobin continued to fall, reaching a low of 46 per cent. *The patient died 4 days after the reaction. Postmortem examination showed de*generative changes in the tubular epithelium of the kidneys and casts of brownish pigmented, hematin material in the lumens of the collecting tubules

In this case there was no clear history of any background for Rh sensitization. However, the patient was a 52 year old woman and presumably had had one or more children. This aspect of the history was not obtained because at that time the importance of normal pregnancies in Rh sensitization was not fully appreciated. As expected, the patient proved to be Rh negative, while the donor whose blood caused the fatal reaction was Rh positive, and the patient's serum contained Rh antibodies, demonstrable by a special technic. While the bloods of the other donors used were not available for testing, it seems reasonable to conclude that some or all of them were Rh positive, and although the earlier transfusions caused no noticeable reactions, they stimulated the production of the Rh antibodies which caused the fatal hemolytic reaction

Aside from the infrequency with which Rh sensitization occurs, the reason the clinical importance of the Rh factor was not discovered sooner is that the ordinary cross-matching tests on glass slides, using saline blood suspensions, *are inadequate to detect the great majority of such incompatibilities.* Only in the exceptional cases, in which the patient's serum contains high-titered Rh agglutinins, will the common slide technic show any clumping of the incompatible donor's red cells A higher percentage of positive reactions could be obtained by incubating the mixture at body temperature for prolonged periods, or by centrifuging to pack the red cells together. Even so, in almost half the cases with clinical evidence of Rh sensitization, no Rh agglutinins can be demonstrated in the patient's serum (7,55). This apparent paradox was explained when the author (56,57) showed that in addition to agglutinins, patients sensitized to the Rh factor may produce specific antibodies possessing the novel property of combining with Rh-positive blood cells but without producing a visible reaction in the usual tests. By devising new tests, such as the blocking and conglutination tests, the author found that the presence of these special Rh antibodies in the sensitized patient's serum is readily demonstrable. Since the fact that a patient is Rh negative is clinically important only if Rh sensitization has

developed, these newer tests, which permit reliable diagnosis of Rh sensitization, constitute an important advance. For this reason, the various tests for Rh sensitization are reviewed here.

Tests for Rh Sensitization

Agglutination Test. In this test for Rh sensitization (58), a drop of the patient's serum is mixed with a drop of a 2 per cent saline suspension of group O, Rh-positive cells* in a small test tube, and the mixture incubated in a water bath at body temperature for 30 to 60 minutes. The reactions can usually be judged from the appearance of the sediment at the bottom of the tube. The sediment is then gently dislodged by twisting the tube and the mixture examined for the presence or absence of agglutination. In positive reactions the red cells are clumped together in masses, usually large enough to be visible to the naked eye, while in negative reactions the mixture remains homogeneous, with each red cell separate and distinct, as proved by microscopic examination. When the patient's serum contains only very small quantities of Rh agglutinin, centrifugation may be necessary to bring out the reaction. On the other hand, when potent agglutinins are present, strong clumping will occur even in tests with the patient's serum diluted with saline solution, and in tests on slides (21) as well as in tubes.

According to our present concept, Rh agglutinins, like other antibodies in general, are modified serum globulins. Moreover, Rh agglutinins, like other hemagglutinins and bacterial agglutinins, are presumably polyvalent (probably bivalent), so that each antibody molecule has more than one specific combining group for the corresponding Rh hapten. Since the red cells presumably have numerous Rh haptens distributed over their surfaces, a latticework forms when agglutinin and agglutinogen combine, with resultant clumping, in accordance with Marrack's hypothesis (59), as illustrated in Figure 1. This concept of the nature of Rh agglutinins is useful in explaining the pathogenesis of congenital hemolytic disease (see pages 463 and 473)

Blocking Test. In searching for an explanation of cases of congenital hemolytic disease which were typical except for the absence of demonstrable Rh agglutinins in the maternal serum, it occurred to me that Rh antibodies might be present, but of a special variety which are incapable of causing agglutination. If such antibodies were allowed to combine with the Rh-positive red cells, the cells might be expected to lose their capacity to agglutinate when anti-Rh agglutinating serum was then added Some

* Preferably two separate bloods of types Rh_1 and Rh_2 should be used for these tests.

encouraging results were obtained in preliminary experiments carried out in 1941, but it was not until 1944, when larger quantities of potent human anti-Rh serum became available for these tests (56), that the existence of such special antibodies, termed "Rh blocking antibodies," was finally proved

Race (60) and Diamond and Abelson (61) encountered these blocking antibodies when pooling anti-Rh_0 and anti-rh' sera in an unsuccessful attempt to produce anti-Rh_0' sera.

In the blocking test (56), a drop of the patient's serum is first mixed with a drop of suspension of group O, Rh-positive red cells and incubated in the water bath. In the absence of Rh agglutinins, no clumping should

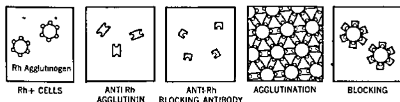


Fig 1 Diagrammatic representation of Rh agglutination and blocking reactions (59).

be evident at this stage. Then a drop of a good anti-Rh agglutinating serum is added, and the mixture is reincubated in the water bath If the patient's serum does not contain any Rh antibodies, strong clumping should now be evident; on the other hand, if the patient's serum contains Rh blocking antibodies, the red cells will remain unagglutinated or the clumping will be distinctly weakened

I have postulated that Rh blocking antibodies, in contrast to Rh agglutinins, are univalent This would account for the ability of these antibodies to combine with Rh agglutinogen and to block the combining sites on the surface of the erythrocytes, but without clumping them (Fig 1). If this concept is correct, it seems reasonable to conclude that Rh blocking antibodies are comprised of smaller molecules than Rh agglutinins. Therefore, Rh blocking antibodies should be able to traverse the placental barrier into the fetal circulation more readily and earlier in pregnancy than Rh agglutinins

Direct serologic proof of the placenta's filtering action, i e , permitting traversal of univalent antibodies but holding back agglutinins, has recently been obtained by the author in cases involving the A and B agglutinogen (132).

This is supported by the clinical observation that the presence of Rh blocking antibodies is usually of more serious prognostic import than the presence of Rh agglutinins without blocking antibodies; for example, there is greater likelihood of *stillbirths when blocking antibodies are present.*

The discovery of the Rh blocking antibodies has also served to explain certain intragroup hemolytic transfusion reactions. In a number of such cases seen recently (54,62), the patients' bloods were Rh negative, but their sera contained no anti-Rh agglutinins, and in the usual compatibility tests the sera of the patients failed to agglutinate the blood suspensions of the donors whose blood caused the reactions. However, the blocking *tests were positive and showed the presence of Rh antibodies of high titer,* thus accounting for the hemolytic reactions.

Conglutination Test. The discovery of the Rh blocking antibodies explains why the classic cross-matching tests have been inadequate to detect all cases of intragroup incompatibility. By modifying the technic of the compatibility test, it is now possible to avoid this pitfall

The new test for Rh sensitization, termed the "conglutination test" (57), *differs from the agglutination test in that the reaction occurs in two stages* instead of one and that a third component, in addition to the Rh antigen and its specific antibody, must be present in the mixture for clumping to occur. This third component, like complement in serologic hemolysis, is absorbed onto the specifically sensitized red cells, making them stick together. However, the third component is distinct from complement—it resists heating at 60 C., it is a colloidal constituent in the plasma (conglutinin), *and is probably identical with the so-called X protein (63),* which is a large molecular complex of albumin, globulin, fibrinogen, and phospholipid. The Rh antibody participating in the conglutination reaction is univalent and is best referred to as Rh glutinin (45), which may possibly prove not to be identical with blocking antibody

The difference between Rh agglutination and Rh conglutination may be summarized as follows.

Rh-positive red cells + {Bivalent Rh antibodies (anti-Rh agglutinins)} ——→ Agglutination

Rh-positive red cells + {Univalent Rh antibodies (anti-Rh glutinins)} + {Conglutinin (X protein)} ——→ Conglutination

While X protein or conglu[illegible]

[illegible]

[illegible] This explains why

conglutination may not occur under the conditions existing in the agglutination test, since the saline used in preparing the red blood cell suspensions and for diluting the patient's serum may suffice to separate the X protein into its constituent parts. The conglutination test is carried out like the agglutination test except that the use of saline or any crystalline solution is scrupulously avoided (57,65). The red cells are suspended in the individual's own plasma or serum, or, more conveniently, in inactivated group AB serum.

Diamond and Denton (67) have recently reported satisfactory results with 20 per cent bovine albumin in place of human plasma or serum as a suspension medium for these tests. Such results, as well as similar successful results with other proteins, can be explained by the tendency of the protein molecules to form colloidal aggregates in concentrated solutions, and thus function as conglutinin. Best results are obtained, however, with natural conglutinin (X protein) as it exists in normal human plasma.

The patient's serum is tested undiluted, in titrations, the serum is diluted with group AB serum instead of saline solution. In my opinion, the slide test of Diamond and Abelson (64,65), and the capillary tube test of Chown (66), when properly carried out, depend for their success on a conglutination reaction rather than on an agglutination reaction, as originally stated by these workers.

In tests for Rh sensitization by the conglutination technic, positive reactions will always be obtained when the patient's serum contains Rh agglutinins or Rh blocking antibodies or both, and occasionally when the other two tests are negative or inconclusive (57,65). The conglutination test is the most reliable indication of the presence or absence of Rh sensitization, for it is always or almost always positive if the patient is sensitized.

The bizarre behavior of congenital hemolytic disease, in that some infants show no signs of hemolysis until several hours or days after birth, can probably be attributed to conglutinin or X protein, the third component necessary for *in vitro* conglutination, and therefore probably important for *in vivo* hemolysis (45). Apparently in these cases X protein does not form in the infant's plasma until after birth, when the profound physiologic changes which occur at this time cause aggregation of plasma proteins into more complex molecules In this connection, Pedersen (63) has found that serum from cow's fetus and from newborn calves and foals contains large amounts of a special globulin of low molecular weight which he terms "fetuin," and which he believes to be one of the precursors of X protein. He also found fetuin in human umbilical cord serum, though in smaller amount.

Other Tests for Rh Sensitization. Coombs, Mourant, and Race (68,69) have recently described a new and ingenious method of detecting univalent Rh antibodies (blocking antibodies or glutinins). The principle of their test is that Rh-positive red cells treated with human serum containing univalent Rh antibodies become coated with antibody globulin; if such sensitized cells are then tested with anti-human globulin precipitin serum they should agglutinate. In fact, this technic did prove to be a sensitive and specific test for Rh sensitization. It was found, moreover, that ordinary anti-human serum precipitins gave as satisfactory results as antiglobulin precipitins. The following precautions must be observed when carrying out the test. (*1*) The red cells, after being treated with the patient's serum, must be washed three times with saline solution in order to remove all traces of human serum from the supernatant which might inhibit the reaction. (*2*) The precipitin serum used for the tests must first be absorbed with packed, washed, pooled human red cells of groups O, A, and B to remove hetero-agglutinins for human red cells. Then the serum must be standardized by titrating it against washed human Rh-positive red cells that have been sensitized with univalent Rh antibody For the tests, a dilution of the precipitin serum is used which gives sharp and specific agglutination (e.g., 1:20)

The various tests for Rh sensitization that have been described are readily adapted for use as compatibility tests before blood transfusions; one must merely substitute the prospective donor's blood for the known Rh-positive blood in tests with the patient's serum. Obviously, the tests will serve to detect incompatibility due to other blood factors as well as Rh. As compatibility tests, perhaps the most useful of the methods mentioned are the ordinary agglutination tests and Diamond and Abelson's (64) slide test. In the latter, a small drop of the patient's oxalated plasma is mixed with a large drop of the prospective donor's whole oxalated blood on a glass slide and the reactions are read within 5 to 10 minutes. The test is somewhat more sensitive if the slide is placed on a special warm stage like the one devised by Diamond and Abelson.

The final proof of compatibility of a prospective donor's blood is the result of the biologic test (70,71) This test is useful in cases in which Rh sensitization may be present, but there is neither time nor are there facilities for carrying out the *in vitro* tests. It should also be carried out in all cases in which the *in vitro* tests are at all equivocal, or if there is the slightest doubt as to the prospective donor's compatibility Thus, the biologic test *supplements* but *does not supplant* the *in vitro* tests In the test, 50 cc. of the prospective donor's blood are injected into the patient by syringe, or are

diluted with saline solution and administered by the gravity method. If no clinical symptoms and no darkening in the color of the patient's plasma occur within 1 or 2 hours after the injection, the patient can be given any quantity of blood from this donor without danger.

Rh Blood Types

The nomenclature used in this section and in the tables is the most recently expanded one, making use at the same time of further simplifications in the symbols for the genes and Rh types (71a).

While our antirhesus immune guinea pig (or rabbit) sera all gave identical results (2), agglutinating the blood of approximately 85 per cent of all white individuals, we soon found that human antisera from Rh-negative patients

TABLE III

CLASSIFICATION OF Rh BLOOD TYPES (59)

Bloods lacking Rh_0				Bloods containing Rh_0			
Type	Reactions with antisera			Type	Reactions with antisera		
	rh′	rh″	Rh_0		rh′	rh″	Rh_0
rh	−	−	−	Rh_0	−	−	+
rh′	+	−	−	$Rh_1(Rh_0')$	+	−	+
rh″	−	+	−	$Rh_2(Rh_0'')$	−	+	+
rh′rh″	+	+	−	Rh_1Rh_2	+	+	+

sensitized to the Rh factor varied in their specificities (2,7,72). As already mentioned, the great majority of the human antisera gave reactions identical with those of the antirhesus sera, and such human antisera are now designated as standard anti-Rh or anti-Rh_0. The variations among human antisera were soon explained by the demonstration of two additional varieties of Rh agglutinins, one giving 70 per cent positive reactions (7,72) and designated as anti-rh′, the other giving 30 per cent positive reactions (8–10) and designated anti-rh″. If blood specimens are tested with all three antisera (anti-Rh_0, anti-rh′, and anti-rh″), eight distinct types of human blood can be identified instead of the two (Rh positive and Rh negative), detected with the aid of standard human anti-Rh serum or animal antirhesus serum alone (6,8). As the author has shown (6), the three Rh antisera detect three corresponding Rh factors, Rh_0, rh′ and rh″, which in combination give rise to at least five Rh agglutinogens instead of one, namely Rh_0, rh′, rh″, Rh_1 (or Rh_0') and Rh_2 (or Rh_0''). These five agglutinogens in combination determine the eight Rh types, which are heredi-

tarily transmitted by means of at least six allelic genes (6) r, r', r'', R^0, R^1, and R^2.

Anyone familiar with the serology and genetics of the four Landsteiner blood groups can readily master the eight Rh blood types First, considering only the reactions of anti-rh' and anti-rh'', these two antisera determine four types of blood entirely analogous, serologically and genetically, to the four blood groups (8). If, in addition, the reactions with anti-Rh_o serum are taken into account, eight types of blood result, as shown

TABLE IV

RACIAL DISTRIBUTION OF THE Rh BLOOD TYPES

Population	Investigators	Number of subjects tested	Frequencies of Rh types, per cent							
			rh	Rh_1	Rh_2	Rh_1Rh_2	Rh_o	rh'	rh''	rh'rh''
Caucasians										
U S A	Wiener (73)	1,000	12.9	54.1	12.8	16.4	2.6	0.9	0.3	0
	Wiener and Sonn (74)	818	13.5	55.6	15.8	12.0	1.7	1.1	0.3	0
	Unger (17)	2,438	14.5	52.5	15.7	13.1	2.4	1.1	0.7	0.02
	Levine (75)	335	14.0	49.9	16.7	14.6	2.7	0.9	1.2	0
England	Race (76)	927	13.6	54.9	12.2	13.7	2.5	0.7	1.3	0
	Race *et al* (77)	154	12.3	54.0	18.2	13.0	0.6	0.6	1.3	0
Australia	Simmons *et al* (78)	350	14.9	54.0	12.6	16.5	0.6	0.9	0.5	0
Porto Ricans	Torregrosa (40)	179	10.1	39.1	19.6	14.0	15.1	1.7	0.5	0
Asiatic Indians	Wiener *et al.* (33)	156	7.1	70.5	5.1	12.8	1.9	2.6	0	0
Negroes, U S A	Wiener *et al* (24)	223	8.1	20.2	22.4	5.4	41.2	2.7	0	0
	Levine (75)	135	7.4	23.7	16.3	4.5	45.9	1.5	0.7	0
Chinese	Wiener *et al.* (29)	132	1.5	60.6	3.0	34.1	0.9	0	0	0
Japanese	Waller and Levine (30)	150	1.3	37.4	13.3	47.3	0	0	0	0.7
	Miller and Taguchi (31)	180	0.6	51.7	8.3	39.4	0	0	0	0
Mexican Indians	Wiener *et al* (27)	98	0	48.0	9.2	41.8	1.0	0	0	0
Indonesians	Simmons *et al* (79)	200	0	74.0	2.5	22.5	0.5	0	0	0.5
Filipinos	Simmons *et al* (79)	100	0	87	2	11	0	0	0	0
Australian aborigines	Simmons *et al* (79)	100	0	53	21	21	4	1	0	0
Papuans	Simmons *et al* (79)	100	0	93	0	7	0	0	0	0

in Table III The types are named after the antisera with which they react (11,12). Type Rh_o reacts with anti-Rh_o but not with anti-rh' or anti-rh'', similarly, type rh' reacts with anti-rh' but not with anti-Rh_o or anti-rh''; and so forth. Blood reacting with anti-rh' and anti-Rh_o but not with anti-rh'' is designated Rh_1 (short for Rh_o') instead of Rh_orh' because the factors Rh_o and rh' in such blood are ordinarily hereditarily transmitted as a unit like the agglutinogens A_1 and A in blood of subgroup A_1 rather than like the agglutinogens A and B in group AB blood. Thus,

in the mating of rh with Rh_1, as a rule, either the children are all type Rh_1, or half belong to type Rh_1 while the remainder are type rh. To be sure, the factors Rh_0 and rh′ will segregate in occasional matings involving type Rh_1 individuals, namely, when the type Rh_1 parent belongs to genotype R^0r', but such cases are rare and have not yet been encountered because of the low frequencies of genes R^0 and r'. For the same reason, blood reacting with anti-rh″ and anti-Rh_0 but not with anti-rh′ is designated as type Rh_2 (or Rh_0'') rather than Rh_0rh″. Types rh′rh″ and Rh_1Rh_2, on the other hand, are so designated because, with rare exceptions, such bloods contain two separate agglutinogens.

The Rh blood types, like the blood groups and M–N types, exhibit striking differences in distribution in various races, and promise to have important applications in anthropology. Some of the findings on the racial distribution of the Rh blood types are summarized in Table IV. (This supplements the data on distribution of the Rh_0 factor, given in Table I.) Chinese, Japanese, American Indians, Filipinos, Indonesians, Papuans, and Australian aborigines are characterized by the virtual absence of type rh; in Negroes, the most striking finding is the high incidence of type Rh_0, which is about 20 times as frequent as in Caucasians. An interesting case is that of the white Porto Ricans in whom the Rh types clearly indicate the presence of an unnoticed Negro admixture. Some correlation between the frequency of the Rh-negative type in the population and the incidence of congenital hemolytic disease is to be expected; thus, Levine and Wong (28) report that this disease is virtually unknown among the Chinese.

Wiener (80) and Haldane (81) have pointed out that iso-immunization in pregnancy against the Rh factor has a selective action, causing the deaths of a certain number of infants heterozygous for the Rh factor. Over thousands of generations, provided there is no other influence to counteract this effect, every population would tend to become either entirely Rh positive or entirely Rh negative, as has actually occurred, for example, in the case of Mongolians, Pacific Islanders, and Australian aborigines The fact that Caucasians have a high percentage of Rh-negative individuals suggests that this race probably arose from the relatively recent crossing of two (or more) populations, one mainly or exclusively Rh negative and another principally Rh positive. To date, however, no population has been encountered with more than 17 per cent Rh-negative individuals. In this connection, Wiener and Wade (82) recently tested 15 chimpanzees and found that their bloods gave reactions corresponding to type rh. (The possibility that these bloods might actually be weak type Rh_0 could not be

excluded entirely.) This finding of a species of anthropoid apes apparently entirely or predominately Rh negative is of interest in relation to this problem

The author's theory of six allelic genes has been tested by studying the Rh blood types in families (5,83–85) and by the gene frequency method (5,73); the findings support the theory in its essential details. Table V presents the results of investigations on the heredity of the Rh blood types in 197 families with 463 children (84). Only two apparent contradictions to the genetic theory were encountered, and in both of these the children

TABLE V

FAMILY STUDIES ON THE Rh BLOOD TYPES (84)

Mating	Number of families	Number of children, types: rh	Rh$_1$	Rh$_2$	Rh$_1$Rh$_2$	Rh$_0$	rh′	rh″	Totals
rh × rh	4	14	0	0	0	0	0	0	14
rh × Rh$_1$	49	25	73	0	0	7	0	0	105
rh × Rh$_2$	16	10	0	20	0	0	0	0	30
rh × Rh$_1$Rh$_2$	15	(1)	18	14	0	0	0	0	33
rh × Rh$_0$	3	3	0	0	0	3	0	0	6
rh × rh′	2	1	0	(1)	0	0	1	0	3
rh × rh″	1	1	0	0	0	0	0	5	6
Rh$_1$ × Rh$_1$	26	5	62	0	0	4	1	0	72
Rh$_1$ × Rh$_2$	21	6	15	7	18	0	2	0	48
Rh$_1$ × Rh$_1$Rh$_2$	27	0	46	8	25	0	0	0	79
Rh$_1$ × Rh$_0$	1	1	0	0	0	0	0	0	1
Rh$_1$ × rh′	3	0	3	0	0	0	0	0	3
Rh$_1$ × rh″	4	1	2	0	3	0	0	0	6
Rh$_2$ × Rh$_2$	22	1	0	4	0	0	0	0	5
Rh$_2$ × Rh$_1$Rh$_2$	6	0	2	8	8	0	0	0	18
Rh$_2$ × Rh$_0$	2	0	0	1	0	4	0	0	5
Rh$_1$Rh$_2$ × Rh$_1$Rh$_2$	10	0	3	1	17	0	0	0	21
Rh$_1$Rh$_2$ × Rh$_0$	2	0	1	1	0	0	0	0	2
Rh$_1$Rh$_2$ × rh′	2	0	1	1	2	0	0	0	4
Rh$_0$ × rh′	1	0	0	0	0	1	1	0	2
Total	197	69	226	66	73	19	5	5	463

proved to be illegitimate. In the statistical test by the gene frequency method, the findings in white individuals have been in good agreement with the theory of six allelic genes In American Indians and Mongolians, however, the calculated sum of the gene frequencies falls short of 100 per [illegible]

Negroes are characterized by an exceptionally [illegible] uals with blood giving weak or intermediate reactions with one or more of

the Rh antisera (88), and this has been attributed to the existence of still other genes in the Rh allelic series, the so-called "intermediate genes." For practical purposes, the theory of six allelic genes has proved adequate, because the gene R^z and the intermediate genes are quite rare among white individuals Under the theory of six allelic genes (6), 21 genotypes are possible, and the genotypes corresponding to each of the eight Rh blood types is readily ascertained, as shown in Table VI. If the gene R^z and the intermediate genes are taken into account, the situation naturally becomes far more complicated.

TABLE VI

THE EIGHT Rh TYPES AND THEIR TWENTY-ONE GENOTYPES

Rh types	Genotypes
rh	rr
rh′	$r'r'$, $r'r$
rh″	$r''r''$, $r''r$
rh′rh″	$r'r''$
Rh_o	R^oR^o, R^or
Rh_1	R^1R^1, R^1r, R^1r', R^1R^o, R^or'
Rh_2	R^2R^2, R^2r, R^2r'', R^2R^o, R^or''
Rh_1Rh_2	R^1R^2, R^1r'', $r'R^2$

The Hr Factor

The literature on the Hr factor is somewhat confused because the early work was done with weak antisera, so that some of the findings were incomplete and misleading Levine and Javert (89) first reported that they had detected in the serum of an Rh-positive mother of an erythroblastotic infant an antibody which had the property of agglutinating all Rh-negative bloods. Because of this property of the serum, the new agglutinable property detected by it was designated as Hr, and the corresponding agglutinin as anti-Hr. Levine reported that his anti-Hr serum gave about 44 per cent positive reactions, and that all Rh-positive bloods not agglutinated by anti-rh′ reacted with anti-Hr On this basis he postulated that Hr and Rh were allelic, without further clarifying his hypothesis He also asserted (90) that Hr incompatibility should be considered as a possibility whenever an Rh-positive mother has an Rh-negative erythroblastotic infant. As will be shown, this latter statement has been contradicted by subsequent findings.

In 1943, Race and Taylor (91) also detected in the serum of an Rh-positive mother of an erythroblastotic infant an agglutinin which reacted with

all Rh-negative bloods, but differed from Levine and Javert's in that it gave 80 per cent positive reactions. As has been pointed out by Wiener *et al.* (92), however, the serum of Race and Taylor detected the same blood property as that of Levine and Javert, the lower percentage of positive reactions obtained by Levine being due to the use of a weaker antiserum which missed bloods heterozygous for the Hr factor. In this review, therefore, the blood property studied by the British investigators will also be designated as Hr.

As postulated by Race *et al.* (77), Hr is a blood factor present in the agglutinogens determined by genes R^2, r'', R^0, and r, but absent from the agglutinogens determined by genes R^1 and r'. From the reactions determined by the six genes (Table VII), the reactions of the 21 genotypes are readily ascertained as shown in Table VIII. In giving the expected reactions with anti-Hr serum, it is postulated that a single dose of a gene positive for Hr determines a weaker reaction with anti-Hr than a double dose of Hr-positive genes (This idea is supported by observations made in tests with weak anti-Hr serum, while in tests with potent Hr antisera it is difficult or impossible to demonstrate the gene-dose effect.) It will be seen that the expected percentage of positive reactions, approximately 80 per cent, closely agrees with that reported by Race and Taylor, and that observed by the author. If only the strong reactions are counted, then the percentage of positive reactions becomes 30 per cent, as reported by Levine This explains the apparent contradiction between Levine's report and that of Race and Taylor Since Hr-negative mothers can only belong to genotype R^1R^1, R^1r' or $r'r'$, they must transmit either an R^1 or an r' gene to every child, and so cannot have any type rh children, contrary to the assertion made by Levine.

TABLE VII

REACTIONS DETERMINED BY THE SIX STANDARD GENES AND GENE R^z

Genes	Reactions with Rh sera			Reactions with Hr antiserum
	Anti-rh'	Anti-rh''	Anti-Rh_0	
r	−	−	−	+
R^0	−	−	+	+
r'	+	−	−	−
R^1	+	−	+	−
r''	−	+	−	+
R^2	−	+	+	+
R^z	+	+	+	−

If the mother of genotype R^1r' has a child of genotype $r'r$, then in tests with anti-Rh_o serum she would be classified as Rh positive and the infant as Rh negative. Perhaps it is such a case which misled Levine and Javert.

The main clinical application of the Hr factor is as a presumptive test for homo- or heterozygosity of type Rh_1 fathers in families with erythroblastotic infants The diagnosis is only *presumptive* because there are five

TABLE VIII

RELATION OF Hr FACTOR TO Rh BLOOD TYPES IN 350 TESTS ON WHITE INDIVIDUALS IN NEW YORK CITY

Rh blood type	Reactions with Rh sera			Genotypes	Reactions with Hr antiserum*	Per cent observed
	Anti-rh′	Anti-rh″	Anti-Rh_o			
rh	−	−	−	rr	Strong	12.3
rh′	+	−	−	$r'r'$ $r'r$	Negative Weak	0 1.1
rh″	−	+	−	$r''r''$ $r''r$	Strong	0 9
rh′rh″†	+	+	−	$r'r''$	Weak	0
Rh_o	−	−	+	R^oR^o R^or	Strong	1.1
Rh_1	+	−	+	R^1R^1 R^1r' R^1r R^1R^o R^or'	Negative (first two) Weak (last three)	19.7 36 9
Rh_2	−	+	+	R^2R^2 R^2r'' R^2r R^2R^o R^or''	Strong	16 0‡
Rh_1Rh_2†	+	+	+	R^1R^2 R^1r'' $r'R^2$ R^1R^z	Weak (first three) Negative	11.7 0 3

genotypes in type Rh_1, while anti-Hr serum merely subdivides type Rh_1 into two parts Hr-negative individuals of type Rh_1 are almost surely homozygous for R^1, while Hr-positive individuals of type Rh_1 are almost always heterozygous and bear gene r The Hr factor is also important be-

cause it accounts for rare cases of congenital hemolytic disease and of intragroup transfusion hemolysis.

The accuracy of the theory of Race *et al.* regarding the Hr factor has been confirmed by family studies (85,93,95) and by the gene frequency method (27,92). Since every gene negative for factor rh′ is positive for factor Hr, it is evident that factors rh′ and Hr are related to each other serologically and genetically like M and N. Therefore, if data are available concerning the frequency of positive reactions given by anti-rh′ serum in a population, one can readily compute the expected percentage of positive reactions with anti-Hr serum (94).

$$Hr+ = 1 - \left[1 - \sqrt{(rh'-)}\right]^2$$

As shown in Table IX, the observed frequencies of Hr-positive reactions obtained thus far, with only three exceptions, agree closely with the theoretically expected values, and these exceptions are probably due in part to the use of anti-Hr sera of low potency.

TABLE IX

RACIAL DISTRIBUTION OF Hr FACTOR AS SHOWN BY TESTS WITH ANTI-Hr′ SERUM

Population	Investigators	Number of subjects tested	Percentage of positive reactions	
			Observed	Expected
Caucasians				
U.S.A.	Wiener *et al.* (92)	239	72.0	80.0
U.S.A.	Wiener (115)	350	80.0	80.0
U.S.A.	Levine (75)	335	80.9	83.1
England	Race *et al.* (77)	154	82.5	81.4
England	Race (76)	927	80.2	80.1
Australia	Simmons *et al.* (78)	225	76.2	78.3
Negroes				
U.S.A.	Wiener *et al.* (24)	49	98.0	97.7
U.S.A.	Levine (75)	135	99.3	97.4
Mexican Indians	Wiener *et al.* (27)	98	55.8	53.8
Indonesians	Simmons *et al.* (79)	100	33.0	31.8
Australian aborigines	Simmons *et al.* (79)	100	55.0	75.0
Papuans	Simmons *et al.* (79)	100	8.0	0

Fisher (96) has postulated the existence of three varieties of antibodies capable of reacting with Rh-negative bloods, corresponding to the three Rh factors. Since the factor detected by the standard Hr serum which we have described here is related to factor rh′ like a contrasting allele, it may also be designated (95) as Hr′. Mourant (97) has encountered an agglutinin in the serum of an Rh-positive mother of an erythroblastotic infant

which gave only 3 per cent negative reactions on Caucasian bloods. Since all the negatively reacting bloods proved to belong to either genotype R^2R^2 or R^2r'', it is evident that this agglutinin corresponded to anti-Hr''. To date, no antibody has been found which gives reactions corresponding to those expected for anti-Hr_0.

Medicolegal Applications

The Rh blood types, like the other known properties of human blood, have two applications in legal medicine: in individual identification, and in disputed parentage

The four Landsteiner blood groups, together with the subgroups of A and AB, give rise to six varieties of blood· O, A_1, A_2, B, A_1B, and A_2B When the three types, M, N, and MN, are taken into account, 18 (6 × 3) combinations are possible. Since every person is also either P positive or P negative, this doubles the number of possibilities (98). If, finally, the 10 types distinguished by the three sorts of anti-Rh sera and standard anti-Hr serum (Table VIII) are counted, a total of 360 (36 × 10) varieties of human blood can be distinguished

Of course, there are considerable differences in the frequencies with which these 360 varieties appear in the general population The most common combination among Caucasians would be group O, type MN, P positive, type Rh_1, Hr positive, with a frequency of (0 43)(0 50)(0 75)(0.34) = 0 055, or approximately 5 5 per cent The rarest combination would be group A_2B, type N, P negative and type rh'rh'', with a frequency of (0.015)× (0 20)(0 25)(0 0001) or 0 000,000,075, or less than 1 in 10,000,000 The type rh'rh'' itself is rare, having an incidence of 1 in about 10,000, and only a single specimen of this type has been tested by the author.* Stratton (99,100) has encountered four persons of this rare type, two of them siblings. It should be mentioned that the number of identifiable serologic varieties among human beings is actually considerably more than 360, because the calculations given above did not include the secretor and non-secretor types, or the rare agglutinogens such as A_3, or N_2

The individual blood properties can be used to prove that a given blood stain did not come from a particular individual, they cannot be used as evidence that a given stain contains the blood of a specific person Thus, if the combination of blood factors in the stain is not identical with that of a given person, that would prove that the stain does not contain his blood, agreement of the types merely means that the stain contains blood of the

* Found by Dr L. J Unger, the only sample in a series of approximately 10,000 tests (Table IV)

same type as the person in question, but the possibility of coincidence can never be excluded. In a similar way, blood tests may in certain cases prove that a certain man or woman is not the parent of a certain child; they can never establish parentage, since compatability of types can be accidental.

With regard to the Rh blood types, the following rules of heredity hold: (*1*) The properties, Rh_0, rh', rh'', and Hr cannot appear in the blood of a child unless they are present in the blood of one or both parents. (*2*) Individuals with blood lacking factor rh' (types Rh_2, rh'', Rh_0, and rh) cannot have Hr-negative children; and Hr-negative parents cannot have children with blood lacking factor rh'.

In addition, contradictions to the following make parentage extremely unlikely though not impossible parents of types Rh_1Rh_2 and $rh'rh''$ cannot have children of types Rh_0 or rh, and parents of types Rh_0 or rh cannot have children of types Rh_1Rh_2 or $rh'rh''$. Exceptions to this rule are theoretically possible in the very rare instance when the individual of type Rh_1Rh_2 carries the rare gene R^z.

Most commonly, blood tests are used to exclude parentage in cases in-

TABLE X

RESULTS OF Rh–Hr AND OTHER BLOOD TESTS IN CASES OF DISPUTED PATERNITY

Case	Putative father	Mother	Children	Interpretation
1*	$ONRh_1rh$	$A_{1,2}MNRh_0$	$OMNRh_0$ ♀	No exclusion
2	A_2MNRh_1rh		$OMRh_1Rh_1$ ♂	No exclusion
3	$A_1MRh_1Rh_1$	$A_1MRh_1Rh_2$	A_1MRh_2 ♂	Exclusion by Rh–Hr tests
4	$BMNRh_1Rh_1$	$OMNRh_2$	$OMRh_1rh$ ♂	No exclusion
5†	(a) $A_2MRh_1Rh_1$ (b) $BMNrh$	$BMNRh_1Rh_1$	$A_2BMRh_1Rh_1$ ♀	Man (b) excluded by A–B–O and Rh–Hr tests
6	$OMNRh_1rh$	$OMNRh_1Rh_2$	$OMNRh_1rh$ ♀	No exclusion
7	$A_1MNRh_1Rh_1$	$OMNrh$	(1) A_1MNRh_1rh ♀ (2) A_1MNRh_1rh ♀	No exclusion
8*†	(a) A_2MRh_0 (b) $OMNRh_2$	$BMNRh_1rh$	A_2BMRh_1rh	Man (b) excluded by A–B–O tests
9‡	$OMRh_1Rh_2$	$OMRh_0$	(1) $OMRh_2$ ♀ (2) $OMRh_1$ ♂	No exclusion
10	$BNRh_2$	$A_1BMNRh_1Rh_1$	A_1NRh_1rh ♂	No exclusion
11	$A_1MRh_1Rh_2$	$OMNRh_1rh$	$A_1MNRh_1Rh_1$ ♀	No exclusion
12	$OMRh_1rh$	A_1Mrh	$OMrh$ ♂	No exclusion
13*	$OMrh$	$A_{1,2}NRh_0$	$A_{1,2}MNRh_1rh$ ♂	Exclusion by Rh tests
14	$BMRh_1Rh_1$	A_1MNRh_1rh	$A_2BMRh_1Rh_1$ ♂	No exclusion

* Negro.
† (a) Husband; (b) *other man*
‡ Man Chinese; woman Negro

volving children born out of wedlock when the mother accuses a certain man of the paternity of her child, and the charge is denied. Previously, a falsely accused man had one chance in three to establish his innocence with the aid of the blood grouping and M–N tests (98) The Rh and Hr tests have raised the chances of proving the innocence of a falsely accused man to more than 50 per cent To illustrate the usefulness in disputed parentage of the Rh and Hr tests in particular, and of blood tests in general, Table X lists a few hitherto unpublished, illustrative cases recently encountered.

Application in Erythroblastosis Foetalis (Congenital Hemolytic Disease)

Levine's discovery (44,55) of the role of the Rh and Hr factors in congenital hemolytic disease has made possible advances in the diagnosis and treatment of this disease. When selecting blood donors for the treatment of erythroblastotic infants, the same general principles apply as for transfusions for the mother, bearing in mind that the infants are passively sensitized while the mothers are actively sensitized to the Rh factor (101–103). The severity of the disease in the infant appears to depend on the quality as well as the quantity of Rh iso-antibodies that pass into its body via the placenta (45) The disease may be so mild that spontaneous recovery occurs, and the condition may pass entirely unnoticed or be mistaken for physiologic jaundice of the newborn, or it may be so severe that the infant is stillborn. In severe cases where the infant is born alive, the infant may appear quite normal at birth, yet within a few hours or days severe jaundice with or without anemia appears and death occurs shortly thereafter. The destruction of the fetal red cells were originally ascribed to maternal Rh *agglutinins*, but many severe or fatal cases were soon encountered without such agglutinins in the maternal serum. This apparent paradox has now been explained by the discovery (56,57) of univalent Rh antibodies, demonstrable by the blocking and conglutination tests.

For transfusing erythroblastotic infants, untreated maternal blood must not be used, since the additional iso-antibodies injected into the infant may increase the severity of the disease. In mild cases, paternal blood will give satisfactory results, in more severe cases, the father's blood or any blood susceptible to the maternal iso-antibodies should not be used, because if an excess of Rh antibodies is present in the infant's serum it could cause hemolysis not only of all the infant's own red cells but also of the additional Rh-positive blood that may be transfused For this reason Rh-negative blood is to be preferred. If Rh-negative donors are not available, the mother's citrated blood can be washed twice with saline solution to free

the red cells of plasma and used for the transfusion. This procedure has the advantage that it can always be used, even in problem cases involving Rh-positive mothers or in instances of multiple sensitization (102,104). Breast feeding should be interdicted, to avoid the risk of the infant's ingestion of additional iso-antibodies in the milk (105–108).

When the maternal antibodies combine with the fetal or infant's red cells, two distinct, harmful effects may result: (*1*) the breakdown of the fetal red cells gives rise to a hemolytic anemia; (*2*) the circulating red cells of the fetus or infant, coated with Rh antibody and possibly with adsorbed X protein, adhere to each other or to the walls of the blood vessels, blocking the circulation to vital organs; or else the blood vessels may be obstructed by agglutinated stromas or other products of red cell hemolysis. The resulting damage to the brain, liver, and other organs causes stupor, deep jaundice, and other signs of toxemia. The anemia and toxemia vary in *degree in different patients and apparently are not correlated, so that* infants without any anemia may nevertheless die from severe toxemia *Infants who would otherwise die from anemia can be saved by timely* transfusions of Rh-negative blood, but ordinary transfusions, unfortunately, *have no beneficial effect in the prevention or treatment of the toxemia*

As illustration, two cases (71) are cited

Case 3. A woman pregnant for the second time gave the history that her first child, a boy now 3 years old, had become anemic shortly after birth (delivery by Cesarean section), and had required a number of transfusions over a period of a month. Blood tests on the patient, her husband, and child revealed the following

Blood of	Group	M–N type	Rh type
Patient	O	N	rh
Husband	O	MN	Rh_1
Son	O	MN	Rh_1

These findings supported the diagnosis of congenital hemolytic disease in the first child, even though no Rh antibodies were detectable in the maternal serum by the tests available at the time * Moreover, it seemed likely that the expected infant would be Rh positive (*subsequent tests showed the husband to be Hr negative*) and therefore susceptible to the maternal iso-antibodies Accordingly, before delivery blood was drawn from a group O, type rh donor in preparation for transfusions to the expected infant This precaution proved life-saving, when *the infant*, a female, was delivered by Cesarean section, it was extremely pale, breathed poorly and was very feeble (*subsequent tests indicated that the hemoglobin concentration*

* Probably antibodies would have bee[illegible] ative conglutination method That the patient [illegible] lished by a biologic test perf[illegible] in agglutinins in her

at birth must have been less than 20 per cent) Transfusion was started immedi- [illegible]

another transfusion of 75 cc. of blood was necessary when the infant was 1 month old. The results of repeated hemoglobin determinations are shown in Figure 2 The partition of the hemoglobin value into that of patient and donor yielded interesting results; for a month, virtually the only red cells in the infant's circulation were those derived from the blood donors,* then, as the donor's red cells disappeared from the circulation, they were gradually replaced by the infant's own red cells, and by the time the infant was 3 months old she had fully recovered, and has been perfectly normal ever since.

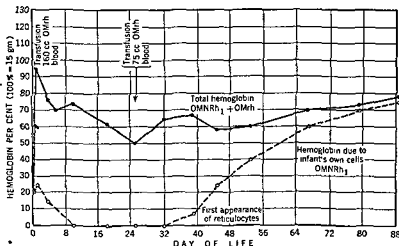


Fig 2 Results of hemoglobin and differential agglutination tests on infant of case 3 (71)

In this case, the condition of the infant was so desperate that as much as 160 cc of blood was transfused at one time. Ordinarily, the maximum amount transfused at a time is 10 cc. per pound of body weight, since the injection of larger amounts might cause dangerous cardiac embarrassment. In any event, there is little to gain by transfusion until the hemoglobin drops to about 80 per cent or lower, the transfusions acting merely to replace hemolyzed blood and having little or no effect on the toxemia Since the

* [illegible]

average newborn infant weighs about 7 pounds and has a blood volume of approximately 250 cc., two or three transfusions of approximately 70 cc. each will usually suffice to maintain the infant's hemoglobin concentration above 60 per cent. In very mild cases, no transfusions may be required or a single transfusion may be sufficient, while in more severe cases as many as five or six transfusions may be necessary.

The case just described is somewhat atypical in that the first infant had congenital hemolytic disease, even though the mother apparently had no history of a blood transfusion. For reasons already discussed (page 443), the first child is usually unaffected unless the mother has received a previous injection of Rh-positive blood (109).

Case 4. The patient, pregnant for the fourth time, was near term when first seen. Her first pregnancy yielded a normal full term male, now 9 years old and well, the second pregnancy terminated with a miscarriage at 10 weeks; the third pregnancy (a few years before the present one) yielded an erythroblastotic infant who died after 4 days. Blood tests revealed the following.

Blood of	Group and subgroup	M-N type	Rh type
Patient	A_1	MN	rh
Husband	A_2B	MN	Rh_1Rh_2
Son	A_1	M	Rh_1

Here again the serologic findings supported the diagnosis of congenital hemolytic disease, though no Rh agglutinins could be detected in the patient's serum (blocking and conglutination tests were not in use when this case was first seen). Since the husband belonged to type Rh_1Rh_2, it seemed fairly certain that the expected infant would be Rh positive (either type Rh_1 or Rh_2) and therefore subject to congenital hemolytic disease.

On delivery, the infant proved to be a robust female, 8 pounds in weight, and normal in appearance except for slight bronzing of the skin. Immediate blood tests on the cord blood showed it to be group A and Rh positive, as expected. Subsequent tests proved that the infant belonged to group A, type N, type Rh_2. A biologic test* done on the mother immediately after delivery, with 50 cc. of group A, type Rh_1Rh_2 blood, was positive, confirming our conclusion that she was sensitized to the Rh factor. Though the infant showed no signs of anemia, smears of the cord blood showed numerous erythroblasts in every field, and the serum was deeply jaundiced (icterus index 45). For this reason an exsanguination transfusion was started. An attempt to withdraw blood from the umbilical cord was unsuccessful, and a total of only 50 cc. of the infant's blood could be obtained by way of the anterior fontanel and deep femoral veins. Simultaneously, about 120 cc of group A, type rh blood were transfused into the internal saphenous vein at the ankle. Because of the difficulties encountered and the splendid appearance of the infant, no further

* This test is no longer used by us to detect Rh sensitization in such cases since reliable results can be obtained with the aid of the simple conglutination test.

treatment seemed necessary and the exchange transfusion was discontinued at this point.

For the first 3 days after birth the infant appeared well, with the hemoglobin concentration between 95 and 100 per cent and the red blood cell count averaging 5,000,000. The only disturbing feature was the persistence of icterus On the evening of the third day there was a slight rise in temperature, the infant appeared lethargic, and refused her feeding Stupor supervened, followed by coma, and the infant died on the morning of the fifth day. At autopsy, enlargement of the liver and spleen, generalized icterus, and kernicterus were the principal gross abnormalities noted

It is evident that this infant did not die from anemia but from toxemia with resulting cerebral damage, as evidenced by the kernicterus found at the postmortem examination. The transfusion of 120 cc. of type rh blood had no apparent effect on the outcome, though possibly if a complete exchange transfusion had been successfully carried out, the development of toxemia might have been prevented. It would be helpful if a reliable test could be developed to ascertain which cases will develop toxemia and which merely anemia, because complete exsanguination transfusion is a difficult and laborious procedure, not without danger to the patient, which should be reserved only for cases which would not respond to less strenuous treatment.*

Role of the A–B Blood Groups

Many earlier workers tried to correlate the occurrence of blood group incompatibility between infant and mother with icterus gravis neonatorum, but this idea was abandoned when it was found that the incidence of heterospecific pregnancies was not appreciably different whether the infant was normal or erythroblastotic Levine and co-workers have shown that approximately 90 per cent of the cases of congenital hemolytic disease are due to incompatibility between infant and mother with regard to the Rh factor. In the exceptional cases in which the mother is Rh positive, some have been found to be due to the Hr factor (55,92,110,111), while in rare [illegible] na- [illegible] the, [illegible] of the exceptional cases appear to be due to incompatibility with regard to the A–B blood group factors. The failure of the earlier workers to perceive the importance of the blood groups in congenital hemolytic disease was most

* Since this review was written, we have succeeded in perfecting a safe and simple method of performing complete exchange transfusions in infants (131)

likely due to the confusion caused by their inability to detect Rh incompatibility, the factor accounting for the bulk of the cases.

Direct evidence of the role of the A–B factors in congenital hemolytic disease has been obtained by Polayes (113), Kelsall (114), Wiener *et al.* (115,116), Boorman *et al* (117), and others who found that in such cases the iso-agglutinin titer of the maternal serum was extraordinarily high—as much as 10 to 20 times the average normal titer, or even higher. Levine (118) observed that when the mother of an erythroblastotic infant is Rh negative her husband belongs to an incompatible blood group in only 25 per cent of the cases, while in cases with Rh-positive mothers the husbands' blood groups are incompatible in 50 per cent of the cases. Probably cases of congenital hemolytic disease due to A–B incompatibility are far more common than appears from the available statistics. The reason for this is that while severe or even fatal cases due to A–B incompatibility are encountered, the great majority of such cases are mild or subclinical, and therefore apt to be overlooked. For example, among 10,000 deliveries Halbrecht (119) encountered 9 cases of typical icterus gravis neonatorum and 60 cases of neonatal jaundice with no or only mild anemia, designated by him icterus precox, but which were probably mild examples of congenital hemolytic disease In 57 of the 60 cases the blood group of the infant was incompatible with that of the mother Finally, it should be mentioned that Henry (120) has also encountered 1 case of congenital hemolytic disease in which sensitization of the mother (group A_1B) to the O factor in the infant's blood (genotype *BO*) was apparently responsible for the hemolysis.

The question arises why A–B incompatibility does not cause severe congenital hemolytic disease more frequently Apparently, natural anti-A and anti-B agglutinins are not harmful to the blood of the fetus because of their low titer, and perhaps because the natural antibodies are made up of large molecules that do not traverse the placenta readily (45,45a). Levine's suggestion that the more severe cases occur only when the infant is a nonsecretor is apparently incorrect, because in every case tested by the author the infant proved to be a secretor

As a rule, this is determined by saliva tests If the saliva contains group substances corresponding to the agglutinogens present in the red cells, the individual is a secretor; if the group substances are absent, he or she is a nonsecretor

In some respects the problems raised by the role of A–B incompatibility in congenital hemolytic disease are analogous to those raised by the use of group O donors as universal donors in blood transfusions

Nature seems to have provided a special mechanism to protect infants

of groups A, B, and AB from the maternal A and B iso-antibodies, namely, the low sensitivity of the A and B agglutinogens in the fetal red cells. This appears to be another case of ontogeny recapitulating phylogeny. In rhesus monkeys reactions are obtained corresponding to the human blood group B (121); however, while anti-A agglutinins are present in rhesus serum, no B agglutinogens are demonstrable in the red cells, the B group substance being confined to the tissues and secretions. Similarly, in other monkeys there is also a reciprocal relation between group substances in tissues and the agglutinins in serum (122), while the blood group agglutinogens are apparently absent from the red cells. Only in anthropoid apes and in man are typical A and B agglutinogens demonstrable in the red cells. Since the agglutinogens are still imperfectly developed in the human fetus at birth, this mechanism diminishes the harmful effect of the maternal A and B iso-agglutinins on the fetal red cells. In the case of the Rh factor this protective mechanism is lacking, but instead the nonexistence of natural Rh sensitivity and the rareness with which acquired sensitivity occurs serve to protect the fetus in the vast majority of cases

In general, the pathogenesis of congenital hemolytic disease due to A–B incompatibility is similar to that due to Rh incompatibility (116) As a rule, the first incompatible infant is spared because the natural anti-A or anti-B iso-antibodies are usually too weak to harm the fetal red cells. However, this pregnancy sensitizes the mother, causing her to produce high-titered, immune A or B iso-antibodies, so that a subsequent infant having the same incompatible agglutinogen is affected Even the first infant may be affected if the mother's natural A or B iso-antibody titer is exceptionally high, or if she has been previously sensitized by injections of material containing A and B group substances, for example, pooled human plasma or serum, or therapeutic horse serum.

Recent work by the author has shown that the quality of the A and B antibodies in the maternal serum is more important than their titer. Thus a low titer of a univalent antibody is more dangerous than a higher titered agglutinin, because the former can traverse the placental barrier more readily (132).

Of special interest are the cases in which the mother is Rh negative and the fetus, in addition to being Rh positive, belongs to a blood group incompatible with that of the mother Here the principle of competition of antigens (123) comes into play, so that properties A and B, which are good antigens in man, tend to suppress the less potent antigen Rh. For example, a group O, Rh-negative mother exposed to antigens A and Rh simultaneously may become sensitized to property A alone, or to both A and Rh,

but not to Rh alone. Since cases of congenital hemolytic disease due to A–B incompatibility are more apt to be mild than cases due to Rh sensitization, an Rh-negative woman is slightly better off if her Rh-positive husband belongs to an incompatible blood group than if he belongs to a compatible blood group. And this explains why only 20 per cent of the husbands of Rh-negative mothers of erythroblastotic babies belong to incompatible blood groups, while in the general population 35 per cent of matings are incompatible (123).

Case 5. Case was referred by Dr. L. J. Unger because the patient, who was Rh negative, had had an infant with congenital hemolytic disease, yet her serum did not contain detectable Rh antibodies even by the sensitive conglutination test. There had been 7 previous pregnancies, all normal. The infant in question, the eighth child, was born on June 22, 1945; jaundice and anemia appeared shortly afterward. A single transfusion of group O, type rh blood was given, and complete recovery followed. Blood tests showed the following.

Blood of	Group	M–N type	Rh type
Mother	O	MN	rh
Infant	B	MN	Rh_1

Agglutination, blocking, and conglutination tests on the mother's serum confirmed Dr. Unger's report concerning the absence of Rh antibodies. Titration of the isoagglutinins by the usual tube technic showed the anti-A titer for A_2 cells to be 8 units, and the anti-B titer 50 units (average normal 50). By the conglutination technic, however, while the anti-A titer was the same, the anti-B titer was 10 times as high. These findings proved that sensitization of the mother to the B factor instead of the Rh factor was the cause of the congenital hemolytic disease in this case

Technic of the Rh and Hr Tests

Since Rh and Hr testing presents problems different from ordinary blood grouping, a brief summary of the technic follows. Fuller details may be found in articles and reviews on the subject (58,124,125).

The antirhesus immune animal sera have the advantage that they can be produced at will, assuming that rhesus monkeys and guinea pigs (or other suitable animals) are available. However, the reactions of the experimental antirhesus sera are weaker than those of the better human anti-Rh sera, so the latter are preferred when available. Moreover, as has already been pointed out, antirhesus sera cannot be used for classifying bloods into the eight Rh blood types, or for testing fetal and infant's bloods. For these reasons, while much of the earlier work on the Rh factor was done with antirhesus serum, now almost all the work is done with human antisera

Before a human Rh antiserum can be used it must first be standardized in order to ascertain its specificity. For this all that is required is standard blood suspensions of types Rh_1, Rh_2, and rh and also some good anti-Rh_o blocking serum. With rare exceptions, human Rh antisera belong to one of the five varieties listed in Table IX. Anti-rh′ can be recognized directly because it agglutinates type Rh_1 blood but not type Rh_2, while anti-rh″ agglutinates type Rh_2 blood but not type Rh_1. Sera anti-Rh_o, anti-Rh_o', and anti-Rh_o'' all agglutinate bloods of types Rh_1 and Rh_2 but not type rh blood and so cannot be differentiated directly unless bloods of the rare types rh′ and rh″ are available. They can be differentiated more readily with the aid of anti-Rh_o blocking serum; if the addition of a small amount of potent blocking serum (e.g., one-fifth of the volume) destroys the reactivity of the serum for Rh_1 and Rh_2 bloods, the serum in

TABLE XI

STANDARDIZATION OF ANTI-Rh AGGLUTINATING SERUMS

Serum number	Testing method	Reactions with test cells			Diagnosis
		rh	Rh_1	Rh_2	
1	Direct	−	+	−	Anti-rh′
2	Direct	−	−	+	Anti-rh″
3	Direct	−	+	+	Anti-Rh_o
	Blocked*	−	−	−	
4	Direct	−	+	+	Anti-Rh_o'
	Blocked*	−	+	−	
5	Direct	−	+	+	Anti-Rh_o''
	Blocked*	−	−	+	

* After addition of anti-Rh_o blocking serum.

question must be anti-Rh_o; on the other hand, anti-Rh_o' serum will continue to react with type Rh_1 blood while anti-Rh_o'' will still react with type Rh_2 blood (Table XI).

After the specificity of the serum has been determined, it should be titrated by mixing progressively doubled dilutions of the serum and the test blood cell suspensions in a series of test tubes, incubating in the water bath at body temperature for one hour and then reading the reactions. The titer of the serum is a reciprocal of the highest dilution that still produces distinct clumping of the test cells. A satisfactory serum should have a minimum titer of 10 to 20 units. For the sake of economy, sera of higher titers may be diluted with saline or compatible sera, but since concentrated serum is more stable than diluted serum, such dilution is preferably carried out shortly before use.

When the serum comes from a patient of group O, A, or B, the iso-agglutinins anti-A, anti-B, or both, must be absorbed or neutralized, if the serum is to be used as a reagent for testing bloods of all four groups. This is most readily accomplished by adding properly prepared, pooled saliva from secretors of groups A and B (126). Saliva collected for this purpose is autoclaved at 15 pounds' pressure for 15 minutes and the coagulated proteins and other suspended material can then be removed readily by centrifuging (127). The autoclaved, slightly opalescent saliva is further diluted with 2 to 3 volumes of sterile saline solution, and this sterile solution is stored in the refrigerator until needed.

Of the three Rh factors, Rh_o is by far the most antigenic and accounts for approximately 90 per cent of the cases of intragroup transfusion hemolysis and congenital hemolytic disease. For clinical work, therefore, it is usually sufficient to perform tests merely with the standard anti-Rh_o serum; if such serum is not available, anti-Rh_o' or anti-Rh_o'' sera usually give a close enough approximation for practical work. For more precise work, and for classifying bloods into one of the eight Rh blood types, three separate sera containing agglutinins anti-Rh_o, anti-rh', and anti-rh'', respectively, are necessary. While pure anti-rh' sera may be obtained from type Rh_2 mothers of type Rh_1 or Rh_1Rh_2 erythroblastotic infants and, similarly, anti-rh'' sera from type Rh_1 mothers, such sera are extremely rare. I have found that anti-rh' and anti-rh'' reagents can be prepared more conveniently with the aid of anti-Rh_o blocking sera from sera anti-Rh_o' and anti-Rh_o'', obtained from type rh mothers who have had erythroblastotic infants of types Rh_1 and Rh_2, respectively. Occasionally such sera contain sufficient natural anti-Rh_o blocker so that they can be used without any special treatment. With regard to anti-Hr sera, these rare reagents are usually obtained from homozygous type Rh_1 mothers who have had erythroblastotic infants.

Almost all Rh and Hr antisera react more intensely and have higher titers at body temperature than at lower temperatures. In addition, titer values by the tube method are generally 4 to 8 times as high as the titer values obtained when using the common, open slide technic. Therefore, the ordinary slide technic with saline suspensions can be used for Rh and Hr testing only if suitable potent sera are at hand. It is far more economical to use the tube incubation technic at body temperature, because weaker agglutinating sera can then be used and stronger sera can be used in dilution.

The author has since succeeded in preparing potent Rh agglutinating sera by immunizing normal male professional donors (134) Within a short time, therefore, ample supplies of these potent sera will be available to satisfy all demands

The discovery that by the conglutination method univalent Rh antibodies, "blockers," cause clumping of Rh-positive cells has opened up an additional potential source of Rh antisera. It should be mentioned that while the conglutination technic renders sera containing Rh_0 blockers useful for Rh testing, pure agglutinating sera give weaker reactions by this technic than by the agglutination method. It is evident also that the Rh_0 blocking antibodies added to anti-Rh_0' to convert it to anti-rh′ will cause clumping by the conglutination technic, so this method should not be used when testing for the eight Rh blood types

Congenital Hemolytic Disease and Icterus Gravis Neonatorum—Two Separate Syndromes

One of the major inadequacies of Levine's theory of the pathogenesis of erythroblastosis foetalis is that it does not explain the mechanism responsible for the various manifestations of the disease in different infants. In my opinion, the *quality* as well as the quantity of the antibody in the maternal serum is of importance in this regard (45) Thus, erythroblastosis foetalis appears to comprise three distinct disease syndromes instead of one. The distinguishing characteristics of the two major syndromes together with the author's proposed nomenclature (128) are as follows:

(a) *Congenital Hemolytic Disease (with Anemia and Hydrops)*. As a rule, in this syndrome the maternal serum contains univalent iso-antibodies (blocking antibodies or glutinins) If only small amounts are present, the infant is usually born alive but with an anemia, or an anemia develops shortly after birth Such cases usually recover without sequelae of any sort after simple blood transfusion therapy When larger quantities of univalent antibody are present in the maternal serum, the disease progresses further *in utero* until the degree of anemia is such that anoxemia of the capillary walls permits blood plasma to exude into the tissue spaces A stillbirth results, or a living infant with hydrops, almost invariably a fatal condition. In these "pale" cases, the characteristic pathologic findings are. extreme anemia, anasarca with ascites and hydrothorax, hepatomegaly and splenomegaly; the microscopic findings are extramedullary islands of hematopoiesis in the liver and spleen, and hemosiderosis of the liver and kidney

(b) *Icterus Gravis Neonatorum (with Kernicterus)* Since agglutinins are presumably larger molecules than blocking antibodies, they only

rarely traverse the placenta during pregnancy; when they do, stillbirths are apt to result. During labor and delivery, due to the increased intrauterine pressure, agglutinins may be milked into the fetal circulation, thus accounting for the onset of the disease after birth. At birth, the infant may appear perfectly normal, but the agglutination of red cells in the smaller vessels causes the formation of agglutination thrombi with resulting damage to the liver, brain, and other organs. The infant develops a deep jaundice with little or no anemia, becomes stuporous, takes its feedings poorly, may have convulsions, with coma and death often supervening. In the rare cases that survive, the infant may develop signs and symptoms of a severe neurologic disorder characterized by choreo-athetosis and muscular rigidity, frequently accompanied by mental deficiency. Postmortem examination in these "toxic" infants, dying shortly after birth, reveals the presence of generalized icterus, splenomegaly, hepatomegaly and kernicterus. The kernicterus is not caused by jaundice per se, but represents an *in vivo* staining reaction of ganglion cells damaged by interference with the circulation. The agglutination thrombi found in the small vessels of the brain, distending the lumens of the vessels, support this idea.

The new concept of two major clinical entities with different pathogenesis helps to solve contradictory reports concerning this problem. Naturally, the prognosis, treatment, and prophylaxis will depend upon the pathogenesis The statement that modern transfusion therapy may only serve to save infants for the worse fate of mental deficiency is misleading. In the author's experience, all the infants (approximately 20) to date saved by such treatment are developing into perfectly normal children. The reason for this is that while those with congenital hemolytic disease (due to univalent antibodies) recover, the ones with icterus gravis (due to bivalent antibodies), who are liable to develop sequelae of mental deficiency or cirrhosis of the liver, fortunately survive only rarely.

In support of this theory of the pathogenesis of erythroblastosis, as proposed by the author, may be cited numerous case reports (128,130) in which the difference between the effects of agglutinins and blocking antibodies is illustrated Confusion in diagnosis may be caused by so-called "mixed" or "intermediate" cases due to the presence in the maternal serum of a mixture of univalent and bivalent antibodies. However, such mixed cases appear to be in the minority, so that most cases should offer little difficulty in classification Table XII presents a statistical analysis of a randomly chosen series of 97 families with erythroblastotic fetuses or infants, showing the correlation between the quality of the maternal Rh antibody and the nature of the clinical manifestation in the infant. The

data demonstrate that univalent Rh antibodies tend to give rise to stillbirths (hydrops), while bivalent Rh antibodies usually cause icterus gravis, as postulated by the theory.

An apparent contradiction to the new theory of pathogenesis is the occurrence of kernicterus in cases in which the maternal serum contains only univalent antibodies. Ordinarily, such antibodies merely coat the red cells; as a result, the red cell envelopes are weakened and the coated cells do not withstand the strain of circulation as well as normal cells. The

TABLE XII

CORRELATION BETWEEN QUALITY OF RH ANTIBODIES IN MATERNAL SERUM AND CLINICAL MANIFESTATIONS IN ERYTHROBLASTOTIC INFANT OR FETUS (133)

Maternal antibody	Number of families	Clinical manifestation in infant or fetus*								
		Stillbirths†			Hemolytic anemia			Icterus gravis‡		
		No of cases	Per cent	Probable error	No of cases	Per cent	Probable error	No of cases	Per cent	Probable error
Bivalent (agglutinin)	25	2	8.0	±3.6	7	28.0	±5.6	16	64.0	±6.4
Univalent (blocker or glutinin)	57	25	43.9	±4.4	24	42.1	±4.4	8	14.0	±3.0
Difference and probable error			35.9	±5.6		14.1	±7.4		50.0	±7.1
Mixed (bivalent and univalent)	15	4	26.7	±7.6	10	66.7	±8.1	1	6.7	±4.3

gradual hemolytic anemia which follows has already been described (page 473). If, however, the infant becomes dehydrated, the resulting concentration of the plasma proteins causes excessive formation of X protein and consequent intravascular conglutination. This then has the same effect as intravascular agglutination.

Conclusions

The essential facts concerning the Rh blood types and Hr factors, and the pathogenesis of intragroup hemolytic transfusion reactions and congenital hemolytic disease (erythroblastosis foetalis) have been disclosed by the investigations of the past five years. Intragroup hemolytic transfusion reactions can now be prevented by the use of Rh-negative or other

suitably selected donors. Some advance has also been made in the treatment of congenital hemolytic disease by blood transfusion, and while no method has been devised to *prevent stillbirths, in infants born alive,* liver and brain damage can be prevented by performing an exsanguination transfusion immediately after birth. Prophylaxis of the disease by Rh testing of prospective husband and wife is not yet practicable. However, some reduction in the incidence of the disease may be attained by being careful to transfuse all Rh-negative girls and women only with Rh-negative blood, and by avoiding indiscriminate intramuscular injections of whole blood, and also by avoiding the indiscriminate injection into females of *materials containing A and B blood group substances.* It may be worth while, in cases where Rh-negative women have sisters with erythroblastotic infants and have themselves married Rh-positive men, to counterimmunize them during pregnancy with a potent but harmless vaccine in order to prevent the development of Rh sensitization.

For this purpose the author has used alternating courses, during pregnancy, of diluted (1:10) triple typhoid and pertussis vaccines, administered subcutaneously. In at least one case, this seems to have been the deciding factor which enabled an Rh-negative mother who had previously lost an infant from erythroblastosis, and whose sister had had stillbirths from the same cause, to give birth to a normal infant, even though the infant was Rh positive. The vaccine does not affect the titer of antibodies already present in the serum, but may help to prevent their reappearance after they have disappeared.

Future investigations must be directed principally to finding means of desensitizing mothers of erythroblastotic infants so that they can in subsequent pregnancies bear perfectly normal children.

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Pernicious Anemia and Other Megaloblastic Anemias

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Introduction

It is perhaps difficult for a younger physician to appreciate how widely the modern approach to pernicious and related anemias differs from that of less than twenty years ago For, in spite of much research and an extensive literature since the early descriptions of pernicious anemia as a pathologic entity by Combe (1824), Addison (1849), and Biermer (1872), it was not until 1926 that the announcement by Minot and Murphy of the success of raw liver therapy led to the new investigational approach which has been so fruitful in our understanding and control of this erstwhile fatal condition.

During recent years, moreover, the very picture of the disease, as commonly met with in clinical practice, has undergone profound modifications. It is now uncommon to see new cases displaying the symptoms and signs still described as characteristic in many textbooks For with early diagnosis and appropriate therapy, such features as marked jaundice, glossitis, and splenomegaly are rare, and gross neurologic complications are becoming less frequent The presence of megaloblasts and punctate basophilia in the blood picture are also now exceptional

It will be recalled that less than twenty years ago the current concept of pernicious anemia was essentially that of a severe anemia of insidious onset and idiopathic origin, with a blood picture showing hyperchromia, macrocytosis, anisocytosis, and poikilocytosis The disease was prone to display a series of spontaneous clinical and hematologic remissions and relapses before the inevitable fatal termination. Gastric achylia was becoming recognized as a common but not necessarily essential accompaniment. The causation was regarded as quite obscure, but in view of the frequency of clinical jaundice and of hemosiderosis at autopsy, wide support was given to the view that the anemia was due to excessive blood de-

struction, possibly as a result of the absorption of bacterial hemolysins from the alimentary tract.

It was well known that at autopsy hyperplasia of the red bone marrow was a constant finding, and that histologically the marrow was characterized by the presence of large numbers of primitive red cells, designated by many hematologists as megaloblasts. Since, however, bone marrow studies were not practiced during life, it will be realized that the clinical diagnosis of pernicious or "primary" anemia was necessarily a loose one according to modern views, and consequently it was applicable to any severe, progressive anemia of unknown origin associated with a macrocytic hyperchromic blood picture.

In modern practice the diagnostic criteria are of course much more precise, and a number of different types of anemia are recognized, all of which would formerly have been diagnosed as pernicious anemia These refinements in diagnosis are largely dependent upon improved technical methods of investigation. It is therefore appropriate at this stage to consider briefly some of these newer technical aids to diagnosis and research. Subsequently, the more important recent advances achieved by the application of these methods will be discussed.

Modern Diagnostic Methods

The newer technical methods of investigation may conveniently be grouped under four heads, namely, (1) the controlled therapeutic trial, (2) refinements in methods of studying the peripheral blood, (3) the study of bone marrow cytology in smears prepared from sternal puncture material, and (4) the application of modern biochemical methods to the investigation of problems such as pigment metabolism, analysis of the gastric juice, and fractionation of the liver principle.

Controlled Therapeutic Trial

Minot and Murphy's dramatic discovery that the continued oral administration of whole liver to patients suffering from pernicious anemia was invariably followed by a rapid remission of their anemia and restoration to health, immediately resulted in the utilization of liver therapy as a diagnostic test. Any severe anemia showing a prompt response to liver therapy justified the diagnosis of pernicious anemia

During the ensuing years, however, it became manifest that macrocytic anemias differing significantly in certain clinical aspects from pernicious anemia also responded to liver therapy, while, conversely, other cases

apparently identical with pernicious anemia were occasionally seen which proved refractory.

The method of therapeutic trial was also promptly exploited in attempts to discover the nature of the therapeutic principle, since the biologic test on human patients has so far proved to be the only reliable method of demonstrating the antianemic principle of liver. Work along these lines soon resulted in the identification of the antianemic principle with certain fractions of liver separable by chemical means. This question is discussed more fully on page 506.

Experiments based on this method were also undertaken with the object of studying the pathogenesis of pernicious anemia.

The classic researches of Castle and his colleagues are now so well known that any detailed reference to them is unnecessary. Castle's hypothesis has withstood the criticisms of the past fifteen years, and is now widely accepted as the most satisfactory explanation of the mechanism underlying the production of pernicious anemia. It is sufficient to recapitulate that, according to this hypothesis, in normal erythropoiesis maturation of the primitive erythroblasts is dependent upon the presence in the blood stream of an "antianemic principle," which is elaborated in the stomach, absorbed from the small intestine, and stored in the liver Its elaboration in the stomach results from the interaction of an "intrinsic factor" secreted by the gastric mucosa with an "extrinsic factor" present in certain protein constituents of the diet. It was shown that in pernicious anemia the intrinsic factor was absent from the gastric juice, and accordingly a deficiency in secretion was held to account for the failure of elaboration of the antianemic principle and of consequent faulty erythropoiesis

The theory also provides a ready explanation of the mechanism of production of other types of megaloblastic anemia due to causes such as nutritional deficiency, faulty absorption, or inadequate storage. It also accords well with the gastric achylia which is now generally regarded as being an invariable accompaniment of Addisonian pernicious anemia.

Methods of Studying Peripheral Blood

Hematology, as generally understood, dates from the introduction of methods for staining blood films In this connection the landmarks were the application of aniline dyes by Ehrlich and later the introduction of modifications of Romanowsky's method, still the most popular. More recent refinements in staining technic have contributed but little of practical value to hematology. The one important development in this field, however, has been the routine adoption of vital staining methods for the

demonstration of immature erythrocytes (reticulocytes) entering the peripheral blood.

Although vital staining of blood cells had been feasible since its introduction by Ehrlich in 1880, the practical implications were not realized until the discovery by Minot and Murphy that the institution of liver therapy in pernicious anemia was promptly followed by a well-marked reticulocyte crisis. This resulted in the general adoption of reticulocyte counts as a control measure, not only in research, but in routine diagnosis and treatment.

Anisocytosis had long been recognized as an indication of disordered red cell production, and it was also widely accepted that a blood film containing many well-stained macrocytes was characteristic of pernicious or "primary" anemia, in contrast with the small, poorly stained microcytes of "secondary" anemia. There were, however, no convenient means of determining these features quantitatively, apart from the restricted value of the color index.

The application by Price-Jones of micrometric and statistical methods to the analyses of the diameter of a red cell population has resulted in a method of recording the degree of anisocytosis, as well as the diameters of the red cells The halometer earlier devised by Pijper provides a rapid and simple method of recording the mean cell diameter. Unfortunately, halometry is only of limited value because of the difficulty in obtaining accurate readings in the presence of marked anisocytosis, which produces blurring of the halos.

The establishment of normal hemoglobin standards and the availability of standardized hemoglobinometers, pipets, and counting chambers now invest the color index with much more significance than was formerly the case

Another important hematologic tool that has come into common use only in recent years is the hematocrit With its aid standard indices, such as mean cell volume, mean corpuscular hemoglobin concentration, and mean cell thickness may readily be determined The use of the hematocrit necessitates the employment of venous blood, but this presents no difficulties if modern anticoagulants, such as heparin or potassium ammonium oxalate mixture, are employed Indeed, the use of venous blood in this way is of great practical convenience, since a whole range of investigations can be performed on one sample Credit should be given to Wintrobe for his pioneer work in this field Although the demonstration in a stained blood film of the characteristic picture of macrocytosis, anisocytosis, and poikilocytosis with ovality of outline may justify a provisional diagnosis of

pernicious or a related megaloblastic anemia, it must be remembered that in cases where an iron deficiency is also present, as in the "dimorphic anemias" seen in pregnancy and malnutrition, a degree of hypochromia may be present which may considerably modify the blood picture. In such cases the determination of the mean cell volume and mean cell hemoglobin concentration by the use of the hematocrit is of particular value.

The determination of the absolute indices should be regarded, then, as a useful routine measure, and one that is essential in doubtful cases.

A low white cell count and the presence of macropolycytes is well known to be a feature of Addisonian pernicious anemia; but in other megaloblastic anemias, such as those seen in pregnancy, a moderate leukocytosis may be present.

Sternal Puncture

With the popularization of the technic of sternal puncture during the last decade, clinical hematology has witnessed a shift in its field of interest from the peripheral blood to the sternal marrow.

Formerly, studies in bone marrow cytology were largely confined to observations on autopsy material and on experimental animals. Consequently, it was seldom feasible for the clinical hematologist to correlate from day to day the picture of his patient's blood with that of the bone marrow. Now, however, not only is this practicable as a valuable weapon in research, but the investigation of the marrow picture may provide most useful and sometimes essential information in routine clinical diagnosis

It must not be inferred from these remarks that the study of the sternal marrow should in any way replace careful observations on the peripheral blood by means of modern technical methods Indeed, in the great majority of cases met with in routine clinical practice, the peripheral blood will provide all the information necessary for a provisional diagnosis. In the exceptional case, however, sternal puncture will yield information of inestimable value in diagnosis, in prognosis, and as a guide to treatment. Accordingly, it is incumbent upon all hematologists to familiarize themselves with this procedure, and upon all clinicians to be aware of its value. It should be appreciated, however, that while the technic of performing a sternal puncture is simple and quickly learned, the cytological interpretation of the sternal marrow films calls for considerable experience and should consequently only be undertaken by those with adequate training and experience.

A description of the technic of sternal puncture lies outside the scope of this article, but it may be mentioned that our practice is to make smears

from fragments of marrow particles present in the material aspirated from the sternum. The technical details are discussed in a paper by Davidson, Davis, and Innes (1943), in which the advantages and disadvantages of this procedure are compared with alternative methods.

It is now generally accepted that the macrocytic blood picture of untreated Addisonian pernicious anemia in the stage of relapse is invariably associated with a bone marrow picture characterized by the presence of numerous megaloblasts. Sternal marrow films made from such cases may be recognized at a glance.

We do not propose to discuss the somewhat polemical field of bone marrow cytology at length, but it may not be out of place to present a brief résumé of our own interpretation of the morphology of the different types of red cell precursor, as seen in stained films prepared from material aspirated from the sternal marrow.

A sternal marrow film from a healthy adult, when suitably stained, presents the following features. Of the nucleated cells, roughly 30 per cent may be identified as red cell precursors. A small proportion of these will be seen to be relatively large cells with deep blue cytoplasm and nuclei having a finely reticulated structure in which remnants of nucleoli are visible Of the various names proposed for these cells "primitive erythroblast" is the one least open to objection. Far more numerous than these cells are the early normoblasts These are smaller, also with deep blue cytoplasm, but with nuclei showing considerable condensation of chromatin The majority of the red cell precursors, however, are late normoblasts characterized by varying degrees of hemoglobination of the cytoplasm and of condensation of the nuclear chromatin These cells accordingly range from the more immature ones, with a greenish blue cytoplasm and showing some evidence of nuclear structure, to mature cells with pink cytoplasm and dense pyknotic nuclei The process of maturation is, of course, accompanied by a progressive diminution in size, so that the mature normoblast is but little larger than its final product, the erythrocyte

In anemias due to iron deficiency, the marrow picture differs from the above in that there is an increased proportion of basophil normoblasts, while in hemolytic anemias the total proportion of red cell precursors is considerably increased with a relative excess of primitive normoblasts

In pernicious anemia in relapse, the marrow picture presents an appearance which differs fundamentally from those described above It is apparent at a glance that there is a considerable increase in the number of primitive erythroblasts which may constitute 30 per cent of the red cell precursors. Moreover, many of these cells are larger than the primitive

erythroblasts seen in health and in other types of anemia, and have more abundant cytoplasm. In some of these cells the primitive character of the nuclear structure is preserved and nucleoli are present, but in others the chromatin is arranged in a loosely woven fashion. When these features are evident, the cell warrants the designation of an "early megaloblast" A considerable proportion of the more mature red cell precursors also differ morphologically from normoblasts of corresponding stages of maturation. The more obvious of these differences are the relatively abundant cyto-

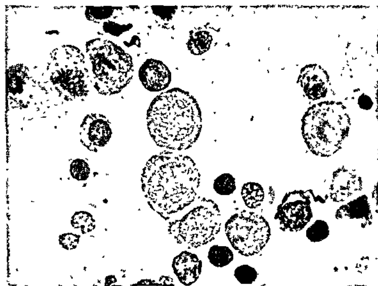


Fig 1 Sternal marrow smear showing megaloblastic erythropoiesis (×800)

plasm and the loosely woven, open character of the nuclear chromatin Even fully hemoglobinated cells may show nuclei with this structure, in contrast with the dense pyknotic nuclei of the mature normoblasts. The term megaloblast is given to any cell of this series displaying the nuclear characteristics outlined above, and it may be qualified by a prefix indicating the degree of maturity, i e, early (basophilic), and late (polychromic or hemoglobinated) megaloblasts

In severe cases of pernicious anemia in relapse, late megaloblasts may occasionally be seen in the peripheral blood Their original description in blood films is attributed to Ehrlich, consequently they are commonly

termed "Ehrlich's megaloblasts" It *should be appreciated, however, that* these cells are merely mature forms of a developmental series.

One should not think that in pernicious anemia all the red cell precursors possess the characteristics of megaloblasts, *since a varying proportion may* be indistinguishable from, and in fact may actually be, primitive erythroblasts and early normoblasts.

Two opposing views are widely held concerning the significance of the megaloblast. According to the older view, the early megaloblast is identical with the primitive erythroblast and is accordingly regarded as a stage in the normal development of the red cell Deficiency in antianemic principle *is held to result in a partial arrest in maturation of the* megaloblasts to the early normoblasts Hence the excess of megaloblasts seen in the bone marrow in various stages of maturation, and the macrocytic *peripheral* blood picture indicative of disordered erythropoiesis.

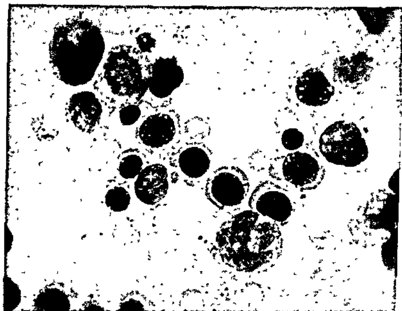


Fig 2 Sternal marrow smear showing normoblastic erythropoiesis (×800)

Supporters of the opposing view maintain that the early megaloblast is essentially a pathologic cell *which only occurs when there is a deficiency of* the antianemic principle In our opinion, cytologic criteria are not sufficiently clear cut to enable the primitive erythroblast to be distinguished

from the early megaloblast with certainty. Fortunately, this matter is mainly of academic interest. One question of practical significance, however, does emerge, namely, should the diagnosis of megaloblastic erythropoiesis be based on a quantitative or a qualitative conception? In other words, what is the criterion for its diagnosis? Is it justifiable to label a marrow picture megaloblastic if only an occasional megaloblast is seen, or must their number exceed some prescribed proportion? It would seem that this question could only be answered by a doctrinal acceptance of one or other of the rival theories.

In our view, scanty primitive red cell precursors with abundant basophilic cytoplasm indistinguishable from early megaloblasts may be seen in marrow films in a wide variety of anemic states, but only in pernicious and related anemias are these cells at all numerous, and only in these types of anemia are seen the late megaloblasts characterized by the typical, loosely woven, open nuclear pattern. The appearances of these cells are so characteristic that the diagnosis of megaloblastic erythropoiesis can readily be made from the inspection of marrow films without resort to differential cell counts

Biochemical Methods

It is not proposed to discuss the application of these in detail, but they may be considered briefly under the following heads.

Gastric Analysis. The association of achlorhydria and pernicious anemia has long been recognized, but only since Castle's pioneer work has its significance been fully appreciated. The introduction of the histamine test has also rendered the interpretation of the test meal much more definite. A histamine-fast achylia is now generally considered to be an essential feature of true Addisonian pernicious anemia, but not of other types of megaloblastic anemia.

A full fractional test meal is usually unnecessary for hematologic diagnosis, because the pertinent point to be determined is whether the stomach is capable of secreting free hydrochloric acid. All that is necessary, therefore, is to secure a specimen of gastric juice after a simple meal such as a glass of water and a cracker. If the examination for free hydrochloric acid is negative, a subcutaneous injection of histamine phosphate should be given and samples of gastric juice removed 15 and 30 minutes later. The demonstration of achylia is of no positive diagnostic value, but the finding of free hydrochloric acid is highly significant in excluding a diagnosis of Addisonian pernicious anemia.

Very rarely, cases labeled with this diagnosis have been reported in which

a histamine-fast achylia was not present. But even if these are accepted, for all practical purposes the presence of free hydrochloric acid in the gastric juice should be regarded as a finding throwing the gravest doubt on a diagnosis of Addisonian pernicious anemia. As already mentioned, in megaloblastic anemias due to causes other than lack of intrinsic factor, free hydrochloric acid may or may not be present.

Studies in Bile Pigment Metabolism. Recent work in this field has thrown considerable light on the fate of the breakdown products of hemoglobin. Tests such as the determination of serum bilirubin, or of urinary and fecal urobilinogen may not be necessary for routine diagnosis, but they provide information of considerable value in research, and in the study of certain varieties of megaloblastic anemia

Other Biochemical Tests. These may provide valuable information, particularly in the investigation of unusual cases, and include procedures that may throw light on the nutritional status of the individual, such as serum calcium and blood sugar estimations, fecal fat analyses, tests for occult bleeding from the alimentary tract, and vitamin estimation tests.

Clinical Examination

A careful history and physical examination must be regarded as an essential feature of the diagnostic investigation. The value of the information derived thereby lies not so much in establishing a positive diagnosis of pernicious anemia as in excluding certain other causes of anemia. For it cannot be overemphasized that the clinical manifestations of anemia result from anoxia affecting all the systems of the body and are modified by its degree and speed of onset rather than by the type of anemia. Consequently, it is relatively seldom that one is justified in making a diagnosis of pernicious anemia solely as the result of a clinical examination. It is true that definite neurologic signs of disease of the posterolateral tracts of the spinal cord in an anemic patient must be regarded as strong presumptive evidence in favor of a diagnosis of Addisonian pernicious anemia, or possibly of a megaloblastic anemia due to severe nutritional deficiency. On the other hand, features such as parasthesia and chronic atrophic glossitis, formerly held to be characteristic of pernicious anemia, are actually met with in clinical practice most frequently as manifestations of the much more common nutritional iron deficiency anemia. Similarly, slight or moderate jaundice and splenomegaly may or may not be present in pernicious anemia, but they are of little diagnostic value since they are also found in other diseases.

The clinical examination may, however, reveal symptoms or signs that

immediately throw doubt upon a diagnosis of pernicious anemia, or may warrant its complete rejection. Thus, a history of recent hemorrhage, infection, dietary deficiency, or residence in the tropics would be of value in giving a clue to the nature of the anemia. The finding of koilonychia, which is practically never seen in pernicious anemia, would be highly suggestive of nutritional iron deficiency anemia, while the demonstration of serious organic disease such as cancer or generalized lymphadenopathy would clearly indicate a disease entity other than pernicious anemia.

It will be appreciated that, in the final analysis, the degree and type of anemia can only be established with certainty as the result of hematologic examination.

Roentgenologic Examination

This is of little diagnostic value in the vast majority of anemias, including pernicious anemia. Nevertheless, it may be essential where ulceration or neoplastic disease of the alimentary tract is suspected, or in obscure cases in which the anemia is due to conditions such as multiple myeloma or metastatic deposits involving the bone marrow. Roentgenography of the skeleton may also provide valuable information in the study of anemic states due to nutritional disorders accompanied by defective ossification.

Classification

It has long been recognized that classic Addisonian pernicious anemia is characterized by a macrocytic blood picture, but now it is becoming generally accepted that a similar blood picture may occur in other types of anemia, some of which may differ fundamentally from the Addisonian variety.

The macrocytic anemias most frequently met with in practice are, however, related to classic pernicious anemia, in that they are associated with megaloblastic erythropoiesis and that, generally speaking, they respond to liver therapy. On the other hand, a macrocytic blood picture may be encountered in anemias which display normoblastic erythropoiesis and are quite unresponsive to liver therapy.

Accordingly, it has become the practice of many authors to designate the anemias of the first group, including Addisonian pernicious anemia, as "megalocytic" anemias, since they result from megaloblastic erythropoiesis. The adoption of this terminology, implying that a megalocyte differs from other macrocytes in that it is derived from a megaloblast, necessarily raises the question as to whether there is any morphologic distinction between these two types of macrocyte permitting their identification by visual inspection. In other words, is it possible to distinguish

a "megalocytic" anemia from other macrocytic anemias solely by examining the blood film?

In our opinion the answer to this question is in the negative. Admittedly, in normoblastic macrocytic anemias the red cells do not usually show so marked an anisocytosis and ovality of outline as seen in cases of megaloblastic anemias of equivalent severity, but these differences are not sufficiently constant or obvious to have them accepted as diagnostic criteria.

Cytologic differentiation between these two groups of anemias, therefore, depends in the final analysis upon examination of the bone marrow by sternal puncture. Accordingly, we prefer to use the more logical term "megaloblastic" rather than "megalocytic" to describe an anemia resulting from megaloblastic erythropoiesis.

In further support of this view the following arguments warrant consideration. (*1*) The etymologic distinction between the terms "macrocyte" (*makros*, meaning long) and megalocyte (*megas*, meaning great) is meaningless as applied to the differentiation between these two cells. (*2*) Megaloblastic anemias of pregnancy, as well as certain other rare types of megaloblastic anemia (Davidson, Davis, and Innes, 1942b; Foy and Kondi, 1943; Rhodes), do not invariably display a macrocytic or "megalocytic" blood picture. In such cases cytologic diagnosis clearly rests upon the marrow cytology (*3*) It is indeed the case that, with rare exceptions, megaloblastic anemias respond to liver therapy in contrast to other forms of anemia which fail to do so. It may accordingly be agreed that the diagnosis of "megalocytic" anemia can be based on the result of liver therapy The term "megalocytic" connotes a morphologic criterion, however, which as already indicated is not warranted by the facts.

We fully admit that in routine clinical practice the performance of sternal puncture is not to be regarded as essential for diagnosis. In the case, for example, of a patient where clinical features and peripheral blood findings are typical of pernicious anemia, it is quite justifiable to base a provisional diagnosis on these findings and to proceed forthwith with liver therapy A satisfactory hematopoietic response would then provide confirmation of the provisional diagnosis In such circumstances, although the diagnosis of the bone marrow morphology is made by inference and not by inspection, we see no objection to describing the anemia as megaloblastic rather than megalocytic.

If a sternal puncture is contemplated, it should be performed before the commencement of liver therapy, for the response to liver therapy results in such a rapid modification of the marrow picture that a retrospective cytologic diagnosis may be impossible This statement, however, does not

apply to cases which fail to respond, since cases of refractory anemia may continue to show typical megaloblastic marrow pictures after repeated injections of potent liver extract

In view of these considerations, we adopt the term megaloblastic anemias for the group of anemias forming the subject of this article. Macrocytic anemias associated with normoblastic erythropoiesis will not be discussed further. But before dismissing this group, it may be mentioned that they are occasionally encountered in the following conditions: leukemia, leukoerythroblastic anemias, certain hemolytic syndromes, hypothyroidism, scurvy, and certain rare refractory anemias of idiopathic origin associated with a hypoplastic bone marrow.

Megaloblastic anemias may be conveniently classified into two main groups, the etiologic basis being regarded as provisional in the light of current knowledge The two groups are: (*1*) Addisonian pernicious anemia, and (*2*) other megaloblastic anemias. The first is caused by defective formation of the intrinsic factor. In addition to the usual clinical and hematologic features, it is characterized by gastric achylia and, in the stage of severe relapse, by a raised plasma bilirubin level. In the second group gastric achylia is not necessarily present and the plasma bilirubin may not be raised The blood picture usually resembles that of Addisonian anemia, but occasionally macrocytosis may not be evident, and if a deficiency in iron is also operating the picture may be hypochromic or "dimorphic," and the color index may be unity or below it

The anemias in this second group can be grouped etiologically as follows: (*a*) defective intake of extrinsic factor, comprising nutritional anemias, especially in the tropics, (*b*) defective absorption of antianemic principle, as in alimentary disorders such as sprue, idiopathic steatorrhea, celiac disease, gastrocolic fistula, (*c*) defective storage or elaboration of antianemic principle, due to liver diseases, such as cirrhosis, (*d*) undetermined mechanism, comprising megaloblastic anemia of pregnancy and puerperium, and certain refractory megaloblastic anemias of unknown origin.

Of these various groups of megaloblastic anemia, Addisonian pernicious anemia is much the commonest in temperate climates In the tropics, however, this condition is exceedingly rare, at least in the indigenous population, while megaloblastic anemias due to defective nutrition or defective absorption are relatively common

Etiology

Intrinsic Factor

Site of Formation. From the time that Fenwick drew attention in 1870 to extensive atrophy of the gastric mucosa in patients dying of

pernicious anemia, it was generally taught that this was a constant pathologic finding. But in 1900 Faber and Bloch, using an improved fixation technic, claimed that gastric changes formerly regarded as pathologic were probably the result of postmortem degeneration. More extensive studies, however, by Magnus and Ungley, by Meulengracht (1939), and by Cox established that a genuine pathologic atrophy confined to the upper two-thirds of the stomach was demonstrable in fatal cases of pernicious anemia. Since this area coincides with the acid-secreting region of the stomach, the anatomic lesion provides a satisfactory explanation for the achylia which is such a significant feature of the disease.

These observations would logically lead to the view that the fundus of the stomach is also the area concerned with the secretion of the intrinsic factor. Difficulty in acceptance of this hypothesis arose, however, from experiments of Meulengracht (1934), who found that preparations made from the pylorus of the pig were active in the treatment of pernicious anemia, while similar preparations made from the fundus were inactive. Moreover, total gastrectomy failed to produce macrocytic anemia in pigs. It was concluded from these experiments that in the pig, if not in other animals, the intrinsic factor was secreted by the pyloric glands and Brunner's glands. It should be noted, however, that Petri *et al.* (1941), working with pigs, found that not only total gastrectomy but also resection of the fundus alone resulted in the disappearance of the antianemic principle from the livers of the experimental animals

Fox and Castle confirmed Meulengracht's results with feeding different regions of hog stomach to pernicious anemia patients, but repeating these experiments with desiccated human stomach, they found the fundic and cardiac areas to be highly potent while the pyloric region was only weakly active.

Consequently, there is now satisfactory evidence for the belief that the immediate cause of Addisonian pernicious anemia is an atrophy and dysfunction of the gastric mucosa, confined mainly to the fundus, which results in a deficiency in, or complete lack of, intrinsic factor and incidentally in achylia It should be noted in this connection that Goldhamer (1936) has produced experimental evidence to indicate that in some cases of pernicious anemia a suboptimal amount of intrinsic factor may be present in the gastric secretion, and that therefore the deficiency may be partial and not necessarily complete This observation may explain why the clinical course of the untreated disease is variable and fluctuating, and why the response of different individuals to the same dose of liver extract may differ widely.

An objection advanced against acceptance of the belief that the production of intrinsic factor is confined to the stomach arises from the fact that pernicious anemia has been but rarely observed to follow gastrectomy in man (Jones). Moreover, despite previous reports to the contrary, Ivy failed to produce this type of anemia by gastrectomy in pigs, monkeys, rats, or dogs. He attributes the positive claims of previous workers to the effects of inadequate diet and defective absorption due to intestinal hurry resulting from the operation

It must be remembered that in man relatively few total gastrectomies have been followed up for more than a year or so, while consideration of the recent evidence that the intrinsic factor is produced in the body and fundus of the human stomach renders it obvious that subtotal gastrectomy cannot be expected to result in the complete cessation of its secretion

The anomalous results obtained by gastrectomy in animals led to the suggestion that various regions of the alimentary tract, other than the stomach, might share in the production of the intrinsic factor. Experimental evidence supporting this suggestion has been advanced by various authors; but it was shown by Dexter, Heinle, Fox, and Castle that the apparent antianemic activity of the intestine was lost if the bowel was first thoroughly washed It would seem, then, that any demonstrable hematopoietic activity of the intestinal tract is due to the passive absorption of preformed antianemic principle.

The identity of the cells concerned with the secretion of the intrinsic factor has not been established with certainty, although W. Jacobson suggested that the argentaffin cells of the stomach might be responsible, since he found them to be absent or reduced in cases of pernicious anemia and sprue coming to autopsy, but present in other types of anemia. Magnus, however, failed to confirm these findings

Nature of the Factor. Although pernicious anemia is characteristically associated with gastric achylia, it has been conclusively demonstrated by Castle that the intrinsic factor is not identical with hydrochloric acid, rennin, pepsin, or lipase. It is thermolabile and has not been demonstrated in secretions other than gastric juice It is generally believed to be an enzyme

Interest has recently been aroused with regard to the possible significance of certain pterins in hematopoiesis The argentaffin cells already referred to have been shown to contain uropterin, and xanthopterin has been found in liver extracts by Jacobson and SubbaRow (1937). Tschesche and Wolf (1936) stated that this substance promoted hematopoiesis in certain experimental anemias in animals The role of pterins in pernicious anemia

is at present, however, purely speculative.

Petri *et al.* (1944) have reported that resection of the fundus of the stomach in pigs leads to complete disappearance of the antianemic principle from the liver, but this can be prevented by the parenteral administration of nicotinic acid. This suggests that nicotinic acid may possibly play some part in the production of the intrinsic factor.

Extrinsic Factor

The general plan followed by various investigators attempting to identify the extrinsic factor has been to administer measured quantities of various food substances together with normal gastric juice to patients with pernicious anemia and to assess the resulting hematopoietic response. The extrinsic factor has thus been demonstrated in the following articles of diet: beef muscle, liver, eggs, wheat germ, rice polishings, and yeast. Formijne has shown that the extrinsic factor is soluble in 70 to 80 per cent alcohol but is destroyed by 96 per cent alcohol. It is insoluble in ether, and passes through an ultrafilter.

Since the extrinsic factor appeared to be distributed only in those food substances that were also good sources of the vitamin B complex, it was thought that a chemical relationship might well exist between it and some other component of the vitamin B complex. Recent work, however, by Castle *et al.* (1944) suggests that the extrinsic factor cannot be identified with any of the known components of the vitamin B complex. Nevertheless, the possibility remains that it may be identical with some as yet unknown component of the complex. (For the significance of folic acid in this connection, see page 541.)

Antianemic Principle

Elaboration and Absorption. It has generally been assumed that the antianemic principle is formed in the stomach by the interaction of the extrinsic and intrinsic factors and that it is absorbed in the upper part of the small intestine. The megaloblastic anemias seen in conditions such as sprue and persistent intestinal hurry would thus be explained by defective absorption.

Formijne, moreover, has shown that mixtures of the extrinsic and intrinsic factors incubated *in vitro* are inactivated by treatment, such as extraction with 70 per cent alcohol, to which the antianemic principle is resistant. He therefore concluded that the synthesis is not the result of a simple test tube reaction, but only takes place *in vivo*, the probable site being within the intestinal wall.

It has long been known that megaloblastic anemia may occur in certain chronic diseases of the liver. This has been attributed to impaired storage function in that organ. It has been suggested, however (e.g., Davidson and Fullerton), that the liver may participate in the final elaboration of the antianemic principle and not act merely as a storage depot. Support for this hypothesis has recently been provided by Copenhaver in some ingenious experiments with Amblystoma embryos. It was found that removal of the liver anlage resulted in the eventual development of anemia which was unaffected by liver therapy; but the grafting of liver tissue into the tails of the animals resulted in restoration of hematopoiesis.

Nature of Antianemic Principle. In the course of investigations which have resulted in the production of ever-increasingly potent liver extracts, many attempts have been made to isolate the antianemic principle. The attainment of this objective would not only be of great theoretic interest, but would clearly be of the greatest practical value, since it would open the way to the synthesis of the active principle.

So far, however, these attempts have been unsuccessful. The precise nature of the active principle is unknown, and even the most highly refined liver extracts available have been shown by West and Moore, who used an electrophoretic technic, to consist of mixtures of active and inactive materials.

In a brief survey of recent work in this field the following investigations are among those meriting consideration. Dakin, Ungley, and West, in the course of their work on the production of a purified liver extract, showed that the active principle is, or is associated with, a peptide having the properties of an albumose; and Tschesche and Wolf (1939) demonstrated that it may be a biuret-negative peptide. Wills, Clutterbuck, and Evans, by treating the crude liver extract, campolon, with ammonium sulfate, obtained two fractions, one of which was therapeutically active in Addisonian pernicious anemia, but ineffective in a nutritional macrocytic anemia produced experimentally in monkeys, while the other fraction cured the anemia of monkeys, but was inert in human anemia.

Jacobson and SubbaRow produced evidence suggesting that the therapeutic activity of liver extract may depend upon a number of factors; a primary factor of unknown nature which, given in adequate quantities, may be therapeutically active by itself, and several accessory factors which, themselves inert, are capable of augmenting the activity of the primary factor. These accessory factors are said to include the following substances: *l*-tyrosine, a complex purine, a peptide, tryptophan, and guanosine.

West states that the active material is in all probability a peptide having a molecular weight of between 5,000 and 10,000, as judged by studies with the ultracentrifuge and graded filter membranes ... o known vitamins, but he suggests ... s ability to comb...

Barfred h... to the action of erepsin does not di... ...y, suggesting that the active principle is not a simple polypeptide.

Megaloblastic Nutritional Anemias

Anemia Due to Defective Intake. An anemia resulting from defective nutrition is usually of the microcytic, iron deficiency type, and accordingly relatively little attention was paid to other types until the demonstration by Wills in 1931 that a macrocytic type of anemia seen in pregnant Indian women was responsive to treatment with autolyzed yeast and with liver.

Since then numerous observers have shown that macrocytic anemia amenable to treatment with substances rich in the extrinsic factor ... the antianemic principle is not only relatively fr... women of the tropics, but ... i in men in both tropic...

The infreq... nancy in W... ...own by Green and Snapper, wh... patients seen in Holland. One of them, however, had recently lived in tropical jungles for some years.

The etiologic factor common to this type of anemia would appear to be a dietary deficiency of the extrinsic factor, which is exaggerated in pregnancy by the extra demands of the fetus The greater frequency of the condition in the tropics is explained by the general lower nutritional level, especially in regard to protein foods, obtaining among ... s of natives in the tropics and the ...

Recent ... Vilter ... wit... While am... have reported tha... in vegetarians

B... studies unfortunately have not been widely reported in this group, but publications by observers, both in the tropics (e.g., Fairley *et al*; Trowell, 1942) and in temperate climates (Moore *et al*, Snapper), describing the appearance of sternal marrow, all agree that the erythropoiesis is megaloblastic and similar to that seen in Addisonian pernicious

anemia It may be noted in this connection, however, that Trowell, working in Uganda, has introduced the term "dimorphic anemia" to describe cases in which a dual deficiency of antianemic principle and of iron results in a macrocytic, hypochromic blood picture and a marrow picture showing numerous early megaloblasts together with many basophil normoblasts.

Although the clinical and pathologic pictures of megaloblastic nutritional anemia may obviously be modified by associated nutritional deficiencies, such as those resulting from avitaminosis, from mineral deficiencies, and by parasitic infections, it is generally believed that the condition is essentially similar to Addisonian pernicious anemia in that it results from a lack of antianemic principle. This view, however, is opposed by Wills and Evans, who consider that there is a fundamental difference between the two types of anemia. In support of this distinction it is argued that nutritional macrocytic anemia is never complicated by lesions of the spinal cord; that it is not accompanied by signs of increased hemolysis; and that it does not respond to treatment with certain fractionated liver extracts highly potent in Addisonian pernicious anemia.

It should be noted that no general agreement exists in respect to any of these arguments For Snapper has reported a number of cases of nutritional megaloblastic anemias in North China with associated cord lesions, and numerous observers in various parts of the world have described examples of this condition with evidence of increased hemolysis. Reference will be made in a later section to reports of the efficacy of concentrated liver extracts in this condition It must be admitted, however, that these cases are often relatively refractory to parenteral liver therapy in doses which would be highly effective in Addisonian pernicious anemia

Anemia Due to Defective Absorption. The most important diseases to be considered under this heading are those characterized by faulty absorption of fats, i e, tropical sprue, nontropical sprue or idiopathic steatorrhea, and celiac disease

These conditions may be accompanied by a microcytic anemia of the iron deficiency type, or by a macrocytic anemia with a blood picture resembling that in Addisonian pernicious anemia and a sternal marrow showing typical megaloblastic erythropoiesis

In a series of 198 cases of tropical sprue, Manson-Bahr and Willoughby found a color index of, or above, unity in every instance; furthermore the Price-Jones curve was typical of Addisonian pernicious anemia in every anemic case investigated. More recently, Castle, Rhoads, Lawson, and Payne found a macrocytic anemia in 93 per cent of 92 cases studied in Puerto Rico, while in each of 22 cases the sternal marrow was found to

be typically megaloblastic. An earlier study based on rib biopsies by Krjukoff yielded similar findings in 11 cases of tropical sprue. It may therefore be concluded that the severe anemia of tropical sprue is essentially megaloblastic in type.

In contrast to these findings, the anemia in celiac disease of temperate climates is seldom severe and when present is usually hypochromic in type, although typical megaloblastic anemia has been reported in a small proportion of cases (Fanconi; Thaysen; Bennett, Hunter, and Vaughan).

With regard to the nontropical idiopathic steatorrhea of adults, the recent literature on the blood and sternal marrow findings is scanty. In our own experience of 19 consecutive cases in which the anemia was moderate or severe, the blood picture was hyperchromic and macrocytic in all cases, but only in 9 of them was the bone marrow typically megaloblastic.

Reference must be made to the condition called "parasprue" which has been reported both in the Mediterranean and Eastern theaters of the present war. In this condition the diarrhea and steatorrhea are held to be a direct consequence of a preceding infection with bacillary dysentery. Although anemia may occur, it is seldom severe. It is stated that the majority of these cases are cured by adequate and early treatment along the lines advocated for tropical sprue.

The etiology of sprue remains obscure in spite of much research during recent years. Gastric achylia is not necessarily present, indeed in the majority of cases free hydrochloric acid is demonstrated in the gastric juice. A history of faulty diet is exceptional. Accordingly, it is justifiable to conclude that the megaloblastic anemia cannot be attributed to lack of either the extrinsic or intrinsic factors.

Biochemical studies have shown the occurrence of faulty intestinal absorption not only of fats, but also of carbohydrates, minerals, glycine, and certain vitamins. There is therefore good circumstantial evidence for the belief that the megaloblastic anemia results mainly from defective absorption of the antianemic principle from the small intestine.

This belief is supported by the occasional development of macrocytic anemia responding to liver therapy in various pathologic conditions of the small intestine, such as chronic dysentery, regional ileitis, intestinal anastomosis, tuberculosis, lymphadenoma, and malignant tumors.

The cause of the insufficiency of the small intestine is quite unknown. Hurst has suggested that the underlying mechanism of the steatorrhea lies in damage to Meissner's plexus from toxic agents or deficiency of some unknown factor leading to paralysis of the muscularis mucosae and consequent failure of the central lacteals of the intestinal villi to empty their

contents of split fats and glycerol. Other theories relate the failure in absorption to defective phosphorylation secondary to advanced insufficiency (Verzár and McDougall), or to deficiency of some member of the vitamin B complex (Stannus).

In practice, it is not always feasible to make a strict distinction between megaloblastic anemias due to defective intake and those due to defective absorption, since chronic malnutrition is apt to lead to disorders of the alimentary tract attended by diarrhea and impaired absorption resulting in a complicated clinical picture in which it may be difficult to dissociate the primary from the secondary etiologic factors. Furthermore, as pointed out by Snapper, prolonged malnutrition may eventually result in defective secretion of the intrinsic factor, so that a condition simulating true Addisonian pernicious anemia may be superimposed upon the original picture

Less frequently the converse may occur, since a chronic alimentary disorder may cause an impaired or abnormal appetite with consequent inadequate dietary intake.

Anemia Due to Defective Storage. The belief that the antianemic principle is stored and possibly finally elaborated in the liver provides a ready explanation for the occurrence of megaloblastic anemia in diseases of this organ Available evidence, however, renders it difficult to assess the frequency with which genuine megaloblastic erythropoiesis does, in fact, occur in macrocytic anemia attributed to hepatic dysfunction.

Wintrobe (1936) in a series of 132 cases of various forms of liver disease found associated macrocytic anemia in 21 9 per cent, but only in cases in which the liver damage was extensive and of long duration, such as cirrhosis In such cases it was shown that the bone marrow was hyperplastic, and the peripheral blood picture resembled that seen in pernicious anemia, although the red cell count was rarely below 2,500,000 per cubic millimeter.

The literature contains many other references to macrocytic anemia in association with cirrhosis and other diseases of the liver, but we know of no reports of the sternal marrow morphology in such cases References to the bone marrow seen at autopsy commonly refer to its being hyperplastic, but detailed cytologic descriptions do not appear to have been published.

Satisfactory hematopoietic responses to injections of liver extracts have been reported by Goldhamer (1934), Wintrobe (1936), and others.

The production of experimental cirrhosis in animals was found to result in a macrocytic anemia by Higgins and Stasney, and by Shumacker and Wintrobe. The latter also recorded a hyperplastic bone marrow picture stated to be similar to that seen in pernicious anemia, but here again it is not clear whether it was actually megaloblastic

There appears, then, to be presumptive evidence that a megaloblastic anemia may occur in chronic severe liver disease, but it is uncertain how frequently the anemia is essentially due to defective liver function rather than to other factors, such as defective diet or impaired absorption, which may well be operative in such conditions as alcoholic cirrhosis.

Anemia of Pregnancy and Puerperium. Since it was shown by Wills (1931) that macrocytic anemia in pregnant Indian women was amenable to oral treatment with substances rich in the extrinsic factor, the so-called pernicious anemia of pregnancy in temperate climates has been attributed by some authors to dietary defects. It is because we are unable to accept this view, and do not regard megaloblastic anemia of pregnancy as being necessarily nutritional in origin, that we accord a separate section to this condition.

It has been shown by Davidson, Davis, and Innes (1942, b) that the so-called pernicious anemia of pregnancy is essentially megaloblastic in type, although the peripheral blood picture may be "dimorphic." Thus, in a consecutive series of 16 cases, although macrocytes were evident in the blood films in every instance, the anemia was normochromic in 8 cases and hypochromic in 2

Other features of this condition are the infrequency of gastric achylia—free hydrochloric acid was present in 10 of 14 of our cases in which gastric analysis was performed—and the temporary nature of the anemia, since once the puerperium is passed and a normal blood picture is restored, treatment becomes unnecessary

The etiology of megaloblastic anemia of pregnancy is still unsettled. A widely held explanation is that the primary cause lies in a temporary failure of the stomach to secrete the intrinsic factor of Castle during the later months of pregnancy (Strauss and Castle, 1933). These authors had in 1932 established the fact that the secretion of hydrochloric acid may be temporarily impaired in a considerable proportion of pregnant women. Other factors held to be of importance are. (*1*) reduced intake of the extrinsic factor consequent upon poor diet, capricious appetite, anorexia, and vomiting, (*2*) impaired absorption from the small intestine due to altered hydrogen ion concentration of its contents secondary to reduced gastric acidity; (*3*) increased demands by the fetus for hematinic principles.

None of these explanations appear to us to be entirely satisfactory, since gastric dysfunction in megaloblastic anemia of pregnancy is no more frequent or marked in degree than in pregnant women with no anemia or with hypochromic anemia Likewise, in many of our cases of megaloblastic anemia of pregnancy the nutritional state and the dietary

history was entirely satisfactory. Finally, we know of no proof that impaired absorption of the antianemic principle from the small intestine actually occurs in pregnancy. If, in fact, this does occur, the question arises why megaloblastic anemia is so rare in pregnant women, the majority of whom show comparable states of failure in gastric secretion. Hence we believe that the etiology of this condition is still obscure. It should be noted that in contrast to Addisonian pernicious anemia, many cases are relatively or completely refractory to treatment with parenteral liver extracts, although they respond promptly to whole liver or proteolyzed liver by mouth The problem of refractoriness to treatment is discussed on page 537.

Anemias Due to Other Causes. *Endocrine Dyscrasias.* A macrocytic anemia may occur in myxedema, but we are unaware of any evidence that it is of a megaloblastic nature It has been claimed, however, that occasional cases may fail to respond satisfactorily to thyroxine unless liver substance is administered in addition. It is of course necessary in all diseases, especially those of a chronic nature affecting elderly patients, to bear in mind the possibility of the coexistence of Addisonian pernicious anemia

Attention has been drawn to the possible influence exerted by the pituitary gland on blood formation Dodds, Hills, Noble, and Williams, as well as others, have shown that the injection of large doses of posterior lobe extracts into rabbits may produce lesions and disturbances of function in the acid-bearing area of the stomach, together with a macrocytic, hyperchromic anemia Snapper, Groen, Hunter, and Witts described cases in which lesions of the anterior pituitary lobe were associated with hypogonadism, gastric achylia, and macrocytic anemia Snapper later described a similar case in China, in which the sternal marrow was shown to be megaloblastic and which responded hematologically to liver therapy. Two more examples were reported by Witts (1942), both responding to liver therapy and in one of which megaloblastic erythropoiesis was proved

While it is possible that in these cases the picture was complicated by a coincidental pernicious anemia, it would seem more probable that the senile degenerative changes involving the gastric mucosa led to a defective production of the intrinsic factor. According to this view, the mechanism of production of this anemia would be identical with that of Addisonian pernicious anemia, and would differ from it only in the remote cause, namely the endocrine dyscrasia.

Apart from the two examples mentioned above, we know of no satis-

factory evidence that megaloblastic anemia is associated with disease of any other endocrine gland.

Vitamin Deficiency. Until recently there was no conclusive evidence, based on bone marrow studies, that megaloblastic anemia results directly from deficiency of any identified vitamin. While the conditioned vitamin deficiencies of sprue and pellagra may be associated with megaloblastic anemia, such anemia is uninfluenced by thiamin, riboflavin, or nicotinic acid. Moore *et al.* have clearly demonstrated the ineffectiveness of various purified vitamins. The recent discovery of the remarkable therapeutic effects of folic acid in various megaloblastic anemias necessitates a reconsideration of the problem (pages 541–545).

There is no evidence that the macrocytic anemia commonly seen in scurvy is accompanied by a megaloblastic marrow picture or that it responds to liver therapy A recent claim that vitamin C may exert an adjuvant effect on the liver treatment of pernicious anemia is discussed on page 523.

Aminopyrine. It was shown by Rhoads and Miller that the administration of aminopyrine to dogs fed a deficient diet resulted in a macrocytic anemia and hyperplasia of the bone marrow The anemia could be prevented or cured by liver extracts. Witts (1941) recorded a case of pernicious anemia which became refractory to liver therapy until it was discovered that the patient was taking aminopyrine Discontinuation of the drug resulted in a prompt and sustained hematopoietic response

While the possible effect of this drug on the granulocytes is, of course, well recognized, it is not known whether it has ever caused megaloblastic anemia It is clear, however, that it may exert a deleterious influence on the treatment of an established case of pernicious anemia

Refractory Anemia. The term "refractory anemia" was introduced by Bomford and Rhoads for anemias of a wide variety of types that were refractory, either temporarily or permanently, to hematinic therapy. Davidson, Davis, and Innes (1943) have shown that on the basis of sternal puncture findings these anemias could be classified into two main groups according to whether erythropoiesis was normoblastic or megaloblastic. The former category includes all varieties of aplastic and hypoplastic anemia, as well as conditions such as aleukemic anemia and leuko-erythroblastic anemia. In general, this group has a bad prognosis and offers little scope for treatment other than the employment of symptomatic and palliative measures The megaloblastic group, on the contrary, which will be considered here, merits a hopeful prognosis, provided one is persistent with energetic antianemic therapy

Cases belonging to this group display varying clinicopathologic features They may occur in association with etiologic factors such as pregnancy, steatorrhea, and liver disease, or they may apparently be of idiopathic origin. The idiopathic cases may resemble Addisonian pernicious anemia in every respect apart from response to treatment, or they may differ from it in that free hydrochloric acid is present in the gastric juice, or that the patient may be younger than is usual in Addisonian pernicious anemia The peripheral blood and sternal marrow findings are in all respects similar to those of megaloblastic anemia responsive to liver therapy. A summary of the cases of idiopathic megaloblastic anemia seen by us during the past 5 years is given on page 536 In all cases the criteria for diagnosis were the demonstration of the typical blood and sternal marrow picture, and absent or considerably delayed hematopoietic response to injections of concentrated and highly potent liver extract.

The cause of the refractoriness is quite obscure, and raises the question whether the failure of response to parenteral liver therapy is due to an additional deficiency of some unknown hematinic factor. This question will be considered further in the section dealing with treatment Reference need be made here, however, to "achrestic anemia" Wilkinson and Israels described a number of cases of megaloblastic anemia resembling pernicious anemia in all respects except for the presence of free hydrochloric acid in the gastric juice and a complete or partial failure to respond to treatment with parenteral liver extracts or with hog's stomach preparation It was concluded that the faulty erythropoiesis was due to failure in utilization of the antianemic principle, since extracts made from the livers of several fatal cases produced a hematopoietic response when administered to cases of pernicious anemia It was emphasized by the authors that no histologic evidence of organic disease was present in the livers examined by them. Presumably, certain of the refractory cases studied by us would be eligible for inclusion in this category

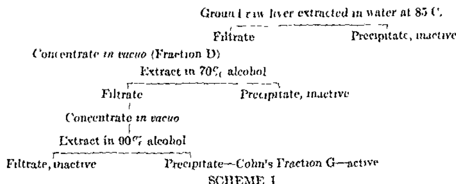
Anemia in Children Although pernicious anemia is extremely rare in children, occasional cases have been reported in the literature In a recent review by one of us (Davis) attention was drawn to the inadequacy of the data supporting a diagnosis of Addisonian pernicious anemia in most of these cases In the same paper, 3 new cases of megaloblastic anemia in children were described, in 2 of which free hydrochloric acid was present in the gastric juice Although none of the children presented objective manifestations of alimentary disorders or histories of dietary deficiencies, retarded somatic development and other features suggested that defective assimilation and possible endocrine dysfunction may have been fundamen-

tal factors in etiology. Moreover, all the cases were refractory to treatment with parenteral liver extracts. One of the cases did eventually respond to prolonged and intensive parenteral therapy, while the other two responded promptly to proteolyzed liver administered orally. For the above reasons the diagnosis of classical Addisonian anemia was rejected, despite the typical blood and bone marrow picture.

Treatment

Antianemic Preparations

Liver Extracts. Shortly after the introduction of liver therapy, the inconvenience of obtaining and administering the requisite daily dose of whole liver resulted in attempts being made to prepare extracts of liver which would be therapeutically potent. Murphy found that a simple water-soluble extract was active, but potent only in relatively large doses. The production of concentrated extracts was first accomplished by Cohn *et al* (1927). The steps employed in extracting a highly potent fraction are represented in Scheme I.



SCHEME I

Cohn's Fraction G forms the basis of most commercial preparations of liver extract available for oral administration. It may be given as a dry powder or as an aqueous solution. It has the advantage of being relatively concentrated in respect to antianemic potency, compared with the amount of whole liver from which it is derived, since during the process of preparation less than 50 per cent of the potent material is lost. The quantity equivalent in potency to half a pound of whole liver is approximately 10 grams of dry extract or 1 fluid ounce of the liquid. Consequently, oral liver extracts are more convenient to take, but they have the disadvantage of increased expense. A further disadvantage at the time of their introduction lay in the variable potency of many commercial preparations.

Following the introduction of oral liver extracts, attempts were made to

prepare more highly concentrated fractions which would be free from harmful substances and thus be suitable for continued parenteral administration. The earliest successes in this direction were obtained by: Cohn, McMeekin, and Minot; West and Howe; and Castle and Taylor These extracts were given intravenously, and suffered from the disadvantages of high cost and a tendency to produce reactions.

Liver extracts suitable for intramuscular injection were first produced in 1931. In that year Strauss, Taylor, and Castle made a suitable extract by dissolving Cohn's Fraction G in water, heating, adjusting to pH 7.4, and adding a suitable preservative. In the same year, Gansslen, working in Germany, reported successful results with intramuscular injection of an aqueous crude extract of fresh liver—campolon

During the ensuing years the reports of numerous observers amply confirmed the reliability and convenience of treatment with liver extracts given intramuscularly It was pointed out by Strauss, Taylor, and Castle that liver extracts given parenterally were over 60 times more effective than the equivalent amount of whole liver given by mouth The earlier parenteral extracts were, however, not highly concentrated, 1 cc. of extract usually being derived from about 5 grams of liver. Accordingly, for maintenance therapy it was necessary to give as much as 20 cc. monthly of certain preparations, although in the case of campolon satisfactory results were obtained from 5 cc monthly.

Subsequent research on liver fractions has been largely directed toward obtaining more highly concentrated, refined extracts, with the result that extracts are now available, 1 cc of which contains active material from more than 100 grams of whole liver. It is not feasible to consider in detail the various steps of the numerous investigators in this field, indeed many are trade secrets, but it is of interest to refer to one of the milestones, namely, the Dakin and West process

These workers in 1935 removed the inactive material in liver with alcoholic calcium acetate, precipitated the active material with Reinecke's acid (tetrathiocyano-diammino-chromic acid), salted it out with ammonium sulfate, and reprecipitated it with magnesium sulfate One gram of the final yield (anahemin) is derived from 100 grams of dry liver extract This preparation was shown by Ungley, Davidson, and Wayne to be of high therapeutic potency.

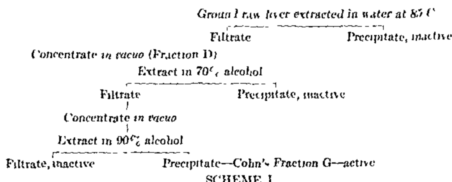
It was also shown by Kyer that charcoal could be used in the concentration of the active material, since it is absorbed on to this substance from which it may subsequently be eluted Charcoal is thus used in the manufacture of a number of commercial extracts.

tal factors in etiology. Moreover, all the cases were refractory to treatment with parenteral liver extracts. One of the cases did eventually respond to prolonged and intensive parenteral therapy, while the other two responded promptly to proteolyzed liver administered orally. For the above reasons the diagnosis of classical Addisonian anemia was rejected, despite the typical blood and bone marrow picture.

Treatment

Antianemic Preparations

Liver Extracts. Shortly after the introduction of liver therapy, the inconvenience of obtaining and administering the requisite daily dose of whole liver resulted in attempts being made to prepare extracts of liver which would be therapeutically potent. Murphy found that a simple water-soluble extract was active, but potent only in relatively large doses. The production of concentrated extracts was first accomplished by Cohn *et al.* (1927) The steps employed in extracting a highly potent fraction are represented in Scheme I



SCHEME I

Cohn's Fraction G forms the basis of most commercial preparations of liver extract available for oral administration. It may be given as a dry powder or as an aqueous solution It has the advantage of being relatively concentrated in respect to antianemic potency, compared with the amount of whole liver from which it is derived, since during the process of preparation less than 50 per cent of the potent material is lost The quantity equivalent in potency to half a pound of whole liver is approximately 10 grams of dry extract or 1 fluid ounce of the liquid Consequently, oral liver extracts are more convenient to take, but they have the disadvantage of increased expense A further disadvantage at the time of their introduction lay in the variable potency of many commercial preparations

Following the introduction of oral liver extracts, attempts were made to

Castle and Strauss, by Conner and McQuiston, and by Klumpp. It has been claimed that it is effective when given by mouth, 1 to 8 teaspoonfuls daily. The first-named authors, however, have stated that it had less potency than the amounts of material from which it is derived, and that it offered no advantage as compared with crude liver. If autolyzed liver was effective in a dose of half an ounce daily we would have thought that this was a real advantage to the patient, as compared with taking half a pound of liver.

Proteolyzed liver is prepared by proteolytic digestion of raw liver with the enzyme papain. A filtrate of the products of digestion is concentrated and dried in a vacuum resulting in a hygroscopic powder of which 1 gram is derived from 6 grams of whole liver. The preparation, available commercially *as hepamino*, was found by Davis, Davidson, Riding, and Shaw to be potent in the treatment of pernicious anemia in daily doses as small as *2 teaspoonfuls (2 drams)*.

The chief value of this preparation, however, is in the treatment of certain types of megaloblastic anemia which are refractory to liver extracts administered parenterally Davis and Davidson have reported a number of such refractory cases, all of which responded promptly to proteolyzed liver. It should be noted, however, that for this purpose a daily dosage of 1 to 2 ounces may be necessary

Hog's Stomach. Sharp, in 1929, showed that hog's stomach contained an antianemic factor. The successful treatment of pernicious anemia with desiccated hog's stomach administered orally was confirmed by Sturgis and Isaacs and by Wilkinson (1930). The average daily dose is 30 grams for treatment and 10 grams for maintenance.

It was shown by Wilkinson and Klein that the active factor, which they name hemopoietin, differs from that in liver extracts in that it is insoluble in 70 to 80 per cent alcohol, is heat labile, and is destroyed by autolysis. Production of preparations suitable for parenteral administration has not proved practicable.

The advantages claimed for desiccated hog's stomach are its cheapness, compared with oral liver extracts, and its effectiveness in cases which are relatively resistant to liver extract (Reznikoff)

Its disadvantages are the considerable variation in potency of many commercial preparations, its heat lability, which prevents sterilization with consequent risk of Salmonella infection (since these organisms may be present in hog tissues), and its unpleasant taste and smell.

Combined Stomach and Liver Preparations. Walden and Clowes showed that digestion of liver tissues or oral liver extract with stomach

The employment of these processes with later modifications has accordingly resulted in the production of many trade preparations which are highly refined and potent in very small doses Since extracts prepared by the older methods are also available, at the present time parenteral liver extracts on the market fall into two main groups, namely, the cruder, less potent ones, and those that are refined and highly potent.

It is necessary to state, however, that no precise definition exists regarding the constitution and method of fractionation for these two groups of liver extract Emery and Hurran, who have recently discussed this question, define a crude extract as one that "has undergone the smallest amount of processing necessary to render it safe for injection. It will therefore normally contain a comparatively large amount of material other than the active principle, and each milliliter will be derived from a comparatively small weight of original liver (2.5 to 10 Gm.) By the term 'refined' we understand an extract that has been derived from a 'crude' extract through several additional stages of manufacture . . . and will be derived from a much larger weight of original liver (50 to 200 Gm) These descriptions may be useful, but they do not express adequately the differences between extracts, and may even lead to the erroneous belief that all the extracts of any one class are similar to each other."

From information at our disposal we can contradict the widely held belief that the content of members of the vitamin B complex is necessarily higher in "crude" preparations than in "refined" ones. It should be understood that fortification of liver extracts by the addition of vitamin preparation does not by itself affect the issue of whether a preparation is to be regarded as "refined" or "crude "

Antianemic activity has been demonstrated in the livers of a wide variety of animal species The livers of many different mammals tested by Aylward *et al.* were all active except that of the sea lion Fish liver was found to be active by Connery, and Davidson (1932) reported the successful treatment of pernicious anemia with fish liver extracts It was hoped that fish might provide a cheap source of material since the liver extract was prepared from the liver residues subsequent to the extraction of the fish oils

In general, however, beef liver has proved the most convenient and cheapest material for the manufacture of extracts

Other Liver Preparations. Autolysis of whole liver after the addition of hydrochloric acid was reported by Herron and McEllroy to result in an increased potency of the antianemic effect of the final product compared with the original amount of liver.

The therapeutic action of this preparation has also been described by

alternative explanation, namely, that the antianemic material derived from yeast may differ from that of meat, not only quantitatively but qualitatively. Ungley and James showed that yeast products exerted no antianemic effect when given parenterally.

It may be concluded that yeast and yeast products do not merit consideration as substitutes for liver or stomach preparations in the treatment of Addisonian pernicious anemia. On the other hand, the use of yeast products in the treatment of nutritional megaloblastic anemias is based on sound theoretic grounds and numerous favorable clinical reports.

A cheap source of autolyzed yeast suitable for the treatment of tropical nutritional anemias has recently been described by Sippe. It is the sediment obtained as a waste product in the manufacture of alcohol by the fermentation of molasses

Other Preparations. Antipernicious anemia activity has been demonstrated, by therapeutic experiments on patients, in organs other than the liver Thus it was recognized to be present in the kidney as early as 1926 by Murphy and Minot, and in brain tissue by Ungley in 1931 The concentration of active material in the kidney is not so high as in liver, and attempts to produce parenteral extracts have not been successful. Reference has already been made to the alleged antianemic activity of the intestine, and to the recent claims that this activity is lost if the bowel be thoroughly washed It may therefore be concluded that liver is the only reliable source of preformed antianemic principle at present available for therapeutic purposes. For the antianemic properties of folic acid and thymine, see pages 541–546.

Potency of Antianemic Preparations

Since the chemical constitution of the antianemic principle is as yet unknown, its therapeutic potency can only be assessed by biologic tests. Furthermore, our ignorance of the nature of the active principle renders it essential that commercial preparations be so tested before they are marketed for clinical use, since uncontrolled variables in process of manufacture may result in considerable variation in the activity of the final product. Indeed, it was this hazard that gave rise to much prejudice against liver extracts before preliminary assay was adopted as standard practice by all reputable manufacturers.

Although many attempts have been made to devise a reliable laboratory test, no satisfactory method has yet been discovered. Observations on laboratory animals, such as pigeons, guinea pigs, rats, and splenectomized rabbits, have shown that the injection of liver material may result in an

tissue resulted in a product having a potency three to four times that of the raw liver used The product is capable of being dried and extracted with alcohol, yielding a powder suitable for oral administration

A commercial preparation has been produced in Sweden, named hepaforte, which is the result of interaction of materials present in raw liver and stomach. According to Sjögren, 10 grams of this substance is equivalent in potency to 250 grams of liver. It is administered in chocolate-coated granules, of which 15 to 45 grams daily have been shown by Odin to provide an effective dose in the treatment of pernicious anemia. For maintenance therapy 5 to 15 grams daily is said to be adequate. It would seem that this preparation provides a convenient means of oral medication, and it is, moreover, claimed to be cheaper than oral liver extracts.

Yeast. It was shown by Wills in 1931 that a commercial preparation of autolyzed yeast, marmite, was effective in the treatment of tropical nutritional anemia, but, as already discussed, this may be regarded as replacement therapy in a condition due to lack of the extrinsic factor. In the treatment of the macrocytic anemia of steatorrhea and sprue, in which the anemia presumably results from defective absorption of the antianemic factor, Vaughan and Hunter, and Castle and Rhoads also claimed occasional successful results with autolyzed yeast

There is no unanimous evidence, however, that yeast is effective in the treatment of Addisonian pernicious anemia Both Goodall and Ungley (1933) obtained hematologic responses in a number of cases, which were, however, frequently suboptimal and delayed Davidson (1933) found autolyzed yeast to be effective in only 2 out of 13 cases, while one of the nonresponsive cases subsequently responded to the administration of yeast products that had been incubated with normal gastric juice Lassen and Lassen treated 8 cases of pernicious anemia with yeast and found it ineffective even when given with normal gastric juice Wintrobe in 1939 reported that autolyzed yeast in doses of 45 grams or more was effective in about one-third of the cases treated, while nonautolyzed dehydrated brewer's yeast, given in very large doses, caused hematopoietic responses in some cases which were equivalent to those produced by oral liver extracts derived from a quantity of liver two to eight times the weight of the yeast used

Observations by Heinle and Miller, who obtained only suboptimal responses, did not confirm those of Wintrobe These authors concluded that the effect of yeast may be attributed to the administration of an excess of the extrinsic factor in the presence of minute amounts of the intrinsic factor which is known to be present in the gastric juice in some cases of pernicious anemia While admitting this possibility, Wintrobe advances an

since the maximal response is to be expected within 7 to 10 days after the commencement of therapy, while the relatively slow rise in the red cell count necessitates a test period extending over 3 or 4 weeks for its acceptance as a criterion of potency. The red cell count has the advantage, however, of being free from certain fallacies attending the reticulocyte response, and is furthermore an actual measurement of the desired therapeutic effect. At the present time, criteria of potency are commonly based upon both the reticulocyte and red cell responses

Reticulocyte Response. For the interpretation of a reticulocyte response it is necessary to remember that a reticulocytosis may occur as the result of many kinds of stimulus to the bone marrow. Thus, a rise in the reticulocyte count may follow administration of drugs such as arsenic in pernicious anemia, iron in cases of iron deficiency anemia, vitamin C in scurvy, and of tissue extracts such as those of the spleen and thymus. A fluctuating, raised reticulocyte count has long been known to be a feature of cases of untreated pernicious anemia going into spontaneous remission.

The reticulocyte response to specific therapy in pernicious anemia has certain characteristics which may now be briefly considered The promptness of the rise in the reticulocyte count and its maximal height is conditioned by the following factors: (*1*) The quantity of active material administered (*2*) The mode of administration, whether by mouth, intramuscularly, or intravenously, and consequently the rate at which the material enters the body (*3*) The initial red cell count, since it is now well established that the height of the reticulocyte response as well as the speed of the red cell regeneration is inversely proportional to the initial count. (*4*) The reactive state of the bone marrow. In elderly patients whose marrows may be hypoplastic, and in patients suffering from conditions such as sepsis, toxemia, or arterial degeneration, the response to treatment may be relatively poor

Within a few days of the commencement of adequate therapy, the reticulocytes show a rapid daily increase in their number reaching a peak or crisis within 7 to 10 days, and thereafter the count rapidly falls to a low level of 1 per cent or so, although the red cell count continues to rise with treatment until a normal figure is reached

The accepted explanation for the transient nature of the reticulocyte response is that the rapid maturation of the megaloblasts during the first few days of therapy results in the expulsion from the bone marrow of large numbers of young immature erythrocytes Subsequently, erythropoiesis proceeds in a more orderly manner and for the most part the young erythrocytes do not leave the bone marrow until they have lost their reticulum,

erythropoietic response indicated by an increase in the reticulocytes in the peripheral blood The consensus of opinion, however, is that such reactions are too variable and inconstant to warrant their adoption as standards for potency of liver extracts intended for clinical purposes. This is not surprising when it is remembered that the action of liver extracts on animals with normoblastic erythropoiesis is fundamentally dissimilar from that exerted in patients suffering from megaloblastic anemias. The use of animals for such purposes would therefore seem to be justifiable only if it ever became practicable to induce in them a megaloblastic anemia comparable with human pernicious anemia

Among the more novel attempts to devise a laboratory test, the effects of liver extract have been observed on the fusion rate of Paramecium caudatum (Middleton and Wakerlin), on the rate of erythropoiesis in chick embryos (Hays, Last, and Koch), and on the migration rate of cells in isolated guinea pig bone marrow preparations (Pace and Fisher). It is unlikely, however, that any of these methods will prove to be of practical value.

In the absence of a reliable laboratory test, it is therefore necessary to rely on patients for purposes of assay. The main disadvantage of the human biologic test is the difficulty in obtaining a sufficient number of suitable patients Clearly, only certain types of patients are eligible. They should be typical cases of uncomplicated Addisonian pernicious anemia reasonably severe in degree, yet not so severe that treatment with preparations of doubtful potency involves a hazard to life Furthermore, it should be known quite definitely that the patient has not received any form of liver therapy during a period of two months or so prior to the test period Since the advent of parenteral liver therapy treatment is being more widely undertaken by the family physician, hence it is easy to understand why suitable cases have become much less plentiful during recent years in the larger clinical centers having facilities for such tests. This difficulty tends to be aggravated by an ever-increasing number of commercial liver extracts needing to be tested. It may well become necessary to institute some form of national or possibly international organization aimed at ensuring that the best possible use be made for test and research purposes of the clinical material available

As is well known, following the institution of specific therapy in pernicious anemia, the earliest hematologic manifestation is a rapid and transient rise in the reticulocyte count accompanied by a slower but sustained increase of red cells, leukocytes, and blood platelets

For test purposes, the reticulocyte count has the advantage of speed,

that this test is only of value if the therapeutic substance is administered daily, and if the first substance to be tested is given in suboptimal doses.

Red Cell Response. As in the case of the reticulocyte response, formulas have been constructed to permit the calculation of the optimal red cell rise over a given period of time.

Riddle, from an analysis of 600 cases of pernicious anemia, devised the formula:

$$I = 0.78 - 0.174\, E_0$$

where I is the average weekly increase in red cells, in millions per cubic millimeter, and E_0 is the initial red cell count. Della Vida and Dyke, after reviewing 125 cases, concluded that more than half gave a response to treatment better than was to be expected from previous formulas, and accordingly suggest the formula:

$$I = 0.93 - 0.214\, E_0$$

the notation remaining the same.

Both Riddle, and Della Vida and Dyke advocate the adoption of the red cell count as the standard criterion for evaluating the response to treatment with antianemic substances, since it is technically simpler than the reticulocyte count, and an optimal red cell response is not invariably preceded by an optimal reticulocyte response and vice versa Indeed, as pointed out by Murphy (1936), the magnitude of the reticulocyte response following injections of liver extract gives merely an indication of the presence of potency, but not the degree of potency

Standardization of Antianemic Preparations. The great variation in concentration of the various liver extracts on the market, as well as the variation in potency of individual preparations, obviously renders it desirable to establish some standard of potency. This has been attempted by the United States Pharmacopeia Advisory Board, for liver, stomach, and other preparations A unit is defined as the minimal amount of material which when given daily in an uncomplicated case of pernicious anemia produces a satisfactory or average reticulocyte response and the relief of anemia and symptoms.

The preparation under test must be administered in uniform daily doses, whether they are given orally or parenterally. In the case of the more concentrated parenteral extracts, it is necessary to dilute the preparation in saline so that the daily dose is not less than 1 cc. The test must be preceded by a control period of at least 2 days, during which daily reticulocyte and blood counts are performed, and the patients must have received no liver or stomach therapy during the preceding 2 months

so that the proportion of reticulocytes seen in the peripheral blood is not necessarily greater than normal.

As the result of the observations of numerous investigators, formulas have been devised to express the optimal reticulocyte response as a function of the initial red cell count. Thus Isaacs and Friedman give the following formula:

$$R = \frac{82 - 22\,E_0}{1 + 0.5\,E_0}$$

where E_0 is the initial red cell count in millions per cubic millimeter.

It should be understood that a reticulocyte response calculated in this way is maximal, and only to be expected if the dosage of antianemic principle is optimal. Suboptimal dosage will result in submaximal responses, but excessive dosage will not necessarily result in a response greater than the optimal. It must also be clearly understood that a submaximal response is not proportional in degree to the dosage of the antianemic substance. Consequently, apart from the implication of a maximal response, the reticulocyte count cannot be used as a quantitative index of potency.

It is generally believed that a maximal reticulocyte response may be expected irrespective of the mode of administration of the antianemic principle, provided the dosage is adequate According to this view, the height of the reticulocyte peak would be the same if a patient were given an adequate dose of whole liver by mouth daily over a period of days or an injection of liver extract of adequate potency at weekly or longer intervals *This assumption is clearly only valid if the dose of liver extract* administered parenterally at, for example, weekly intervals is not less than the aggregate of that contained in a week's supply of whole liver The significance of this argument will be discussed in connection with *the question* of standardization on page 517.

Double Reticulocyte Response. Minot and Castle, whose *paper on* the reticulocyte reactions should be read by all interested in this subject, showed in 1935 that the daily administration of antianemic principle in suboptimal doses results in a submaximal reticulocyte response, and that if subsequently the dosage is increased, a second reticulocyte response occurs.

The exploitation of this phenomenon is clearly of practical value in the evaluation of the comparative potency of two therapeutic products Thus, if the substitution of product B for product A results in a second reticulocyte response, provided the daily dose remains the same, then it may be concluded that B is more potent than A It must be appreciated, however,

Our second criticism is that the test is based upon the principle of daily dosage. In the days when oral therapy was general, such a requirement would have been clearly desirable; but at present approved treatment of pernicious anemia consists of injections of highly potent liver extract given at intervals commonly spaced a week or so apart. With adequate dosage such treatment results in maximal reticulocyte and red cell responses. Our own observations, however, indicate that if liver extract be diluted and given in daily doses in such a manner that each dose contains one-seventh of the amount that would ordinarily be given at weekly intervals, the resulting reticulocyte response is commonly suboptimal in degree and prolonged in duration, although the red cell count may have shown a satisfactory rise by the end of the test period.

This is in fact what we would have expected from our studies on the cytologic changes in the sternal bone marrow following injection of liver extract. An adequate quantity given in one injection results, within 48 hours, in a rapid and massive transformation of the marrow picture from megaloblastic to normoblastic erythropoiesis, providing a satisfactory explanation for the sharp reticulocyte crisis seen in the peripheral blood. When smaller doses of liver extract are given daily the transformation to a normoblastic marrow picture occurs more gradually, providing a reasonable explanation why a smaller but more prolonged reticulocyte response should result In both instances, at the end of 14 days the final state of the marrow picture and the relative extent of red cell regeneration may be identical. Our personal experience, therefore, makes it difficult for us to understand how optimal reticulocyte rises can be obtained when the liver extract under test is administered in small daily doses. Furthermore, it appears to us to be unnecessarily cumbersome to insist upon test conditions which do not correspond with those obtaining in clinical practice

The difficulties in obtaining a sufficiency of clinical material suitable for test purposes have already been referred to, and in our opinion provide a strong argument for the adoption of some simple and more practical criterion of potency. Moreover, in view of the absence of any exact quantitative method of standardizing the antianemic effect of the various liver and stomach preparations, we feel that the use of the term "unit" is apt to imply a somewhat spurious notion of accuracy.

In view of these considerations we would favor the adoption of a standard test for parenteral liver extracts, based upon the weekly injection of stated quantities As the result of such a test, an official certificate could be granted stating that x cc. given at weekly intervals had resulted in a reticulocyte rise and an optimal red cell response.

During the test period a daily reticulocyte count is required until 3 days after it has returned approximately to the pretreatment level, and data covering the red cell count and hemoglobin must be obtained at least twice a week during the first 3 weeks of treatment.

If the test on at least 3 suitable cases results in reticulocyte and red cell responses satisfying certain stipulated criteria, then a certificate of unitage is granted, the material in each daily dose being considered to constitute 1 U.S.P. unit. If the material was diluted before administration, the appropriate correction is made. Thus, if a parenteral liver extract satisfies the test when it is diluted 1 in 10 and given in a dose of 1 cc. daily, the preparation would be considered to have a strength of 10 U.S.P. units per cc. Certain commercial preparations have been certified to contain up to 15 U.S.P. units per cc. but the Advisory Board will not at present assign a strength greater than this, because of the possibility that higher fractionation may cause a loss of unknown factors of therapeutic value. It will be appreciated that the assignment of unitage is based on a standard of minimal performance. Consequently, a given preparation may in fact be more potent than its certificate would imply.

The establishment of the U.S.P. unit has certain obvious advantages; it ensures that a certified preparation is therapeutically active and it provides the clinician with a reliable guide to the appropriate dosage. Obviously, there is a real danger in routine practice if the dosage is limited to the unitage certified for the product employed, since it is well known that individual cases of pernicious anemia may vary quite widely in their therapeutic requirements. Nevertheless, if routine dosage is based upon some such empiric minimum as the equivalent of 2 to 3 U.S.P. units daily, the physician will readily be able to decide the appropriate dosage for any particular certified preparation. Without such a guide he may fall into the error of prescribing inadequate amounts of any of the cruder liver extracts or alternatively of giving excessive and wasteful amounts of a highly refined extract.

There appear to us, however, to be certain disadvantages associated with the U.S.P. standard unit. In the first place, the certificate may be granted as the result of tests on selected cases giving an optimal performance. Not only may this lead to a fallacious belief on the part of the physician that similar therapeutic results may be obtained in average cases, but it perhaps confers an undue advantage on those manufacturers of liver extracts who may have the facilities for obtaining tests on large numbers of patients, from which a few displaying exceptionally good responses may be selected for purposes of certification.

rooted objection to injections, or who may live under geographic conditions rendering injections difficult or impracticable, and patients who develop sensitivity to parenteral liver extracts where it is not feasible to desensitize them Under such circumstances oral treatment with whole liver, or a reliable extract or preparation such as proteolyzed liver or a hog's stomach preparation, may be regarded as a legitimate alternative to parenteral therapy.

Intravenous therapy has little to recommend it. For obvious reasons it is unsuitable for maintenance purposes, while for initial treatment it has the grave disadvantage of a not inconsiderable risk of producing serious protein reactions. It has been advocated for the initial treatment of very severe cases where its acceleration of the response by even a few hours might be an advantage. In such cases, however, when the patient's life is in danger, the paramount need is for blood transfusion, the results of which will render the speed of intravenous medication an advantage of secondary importance. Accordingly, it is doubtful if intravenous liver therapy has any place in modern therapeutics. It should be mentioned that Mulholland has claimed successful responses to intravenous therapy in cases resistant to intramuscular injections.

Although claims have been made that the cruder and less concentrated liver extracts have certain therapeutic advantages over the more highly refined ones, the recent literature fails to provide any convincing evidence of such an advantage in the treatment of uncomplicated cases of Addisonian pernicious anemia. On the contrary, the more highly concentrated preparations would appear to have the advantage of convenience, speed, and economy.

In the United States a number of preparations are available having a certified potency of 10 to 15 U S.P units per cubic centimeter British liver extracts have not yet been issued with certificates of potency, but there are a number of reliable brands which give optimal responses when given in doses of 1 to 2 cc at fortnightly intervals, which we believe would make them eligible for a similar unitage

As already noted, it is essential for the physician to remember that individual patients may vary considerably in their responsiveness to the active principle It is therefore highly undesirable that a new patient should be treated with the minimal dosage that might be expected theoretically to produce an optimal response. In routine practice it is desirable that initial treatment should err on the side of excessive dosage, since this will ensure a prompt response and any excess of active principle over and above that utilized by the patient is probably stored and drawn upon later on.

We are doubtful, furthermore, whether evidence of a prescribed optimal reticulocyte response should be insisted upon for certification. For although we are fully aware of the importance of this reaction in clinical research and as a guide to the treatment and diagnosis of the individual patient, we question whether the demonstration of a maximal response provides any essential information, additional to that derived from the red cell rise, for the purposes of certification of potency. If a preparation is shown to give a satisfactory red cell rise at a given dosage, there would seem to be no sound reason for rejecting it because the reticulocyte response fell short of the theoretic maximum.

Clinical Treatment of Addisonian Pernicious Anemia

In the Stage of Relapse. The leading contributors to modern hematologic literature are almost unanimous in recommending that, in general, the treatment of choice for pernicious anemia is the intramuscular injection of concentrated liver extracts. With this view we are in full agreement, and believe this form of treatment to be superior to oral therapy for the following reasons

Effectiveness. It was originally shown by Strauss, Taylor, and Castle that the intramuscular injection of liver extract derived from 10 grams of liver was as effective as an amount of Cohn's Fraction G derived from 600 grams of liver given by mouth Subsequent observations have confirmed that the active principle is 60 to 100 times as effective when given intramuscularly as when given by mouth The reason for this is unknown Possibly the wastage of material given by the oral route is due to destruction by enzymes in the alimentary tract, or to poor absorption

Economy. It follows from the above that both for initial treatment and maintenance purposes an adequate amount of active principle can be given with much less expense in the form of parenteral liver extracts than by any available form of oral therapy

Convenience. The majority of patients find it less irksome to have injections, which for maintenance purposes usually need be only at monthly intervals, than to have to take half a pound of whole liver or some other preparation each day by mouth.

Reliability. With parenteral treatment the physician in charge of the case has certain knowledge that the patient is receiving adequate treatment, but he has no such assurance if it is left to the patient to take his liver or other preparation by mouth.

In our view, oral therapy should be reserved for a small class of patients for whom it has peculiar advantages This concerns patients having a deep-

treatment. For it must be appreciated that macrocytosis and hyperchromia are signs of pathologic erythropoiesis even in the presence of a hemoglobin reading or a red cell count which may be deemed satisfactory.

The appearance of any of the clinical features mentioned above, or a deterioration in the blood picture, calls for a detailed physical examination in which any objective abnormalities should be noted, and for energetic intensification of liver therapy which should be persevered with until complete clinical and hematologic remission is attained.

In support of these recommendations for treatment it may be of interest to cite a few reports from the more recent literature. Thus, Murphy and Howard maintained a group of 133 patients at a level of 5,000,000 red cells per cubic millimeter over periods ranging from 6 months to 6 5 years with intramuscular injections at average intervals of 3 7 weeks The intervals, however, needed to be reduced to an average of 2 4 weeks in the case of 27 patients above the age of 70

Alt and Young successfully treated a group of 35 patients over periods ranging from 6 months to 8 years with injections at average intervals of 2 to 3 weeks. Their doses were 3 cc of a preparation containing 6 or 10 U.S.P. units per cubic centimeter, and 1 cc. when a highly concentrated extract containing 15 units per cubic centimeter was used Highly concentrated extracts were found to be as effective as the cruder ones.

Evans and Jordan also found a highly concentrated liver extract to be effective in the treatment of 40 cases of pernicious anemia over a period of 4 years

Strauss *et al* (1942) report a 9 years' study of 80 patients with pernicious anemia A uniform maintenance dose of a highly purified liver extract containing 15 U S P. units given every 4 weeks was found to be effective. These authors recommend that a red cell count persistently below 4,000,000 per cc calls for a weekly dose of 30 to 75 units for 2 to 3 months; glossitis or the progression of neural symptoms calls for an increase in the maintenance dose irrespective of the blood count, and finally, if a patient feels in better health when unknown to him the dosage is increased, the original dose should be regarded as suboptimal.

Advantages have been claimed for the employment of massive doses of liver extract at prolonged intervals in the treatment of pernicious anemia. Thus, for example, Askey contends that optimum therapeutic results may be achieved by giving a dose which should theoretically contain the quantity of active principle lacking in the liver together with the amount needed for immediate tissue repair. He treated 22 patients with a single massive dose containing 150 to 400 U.S.P. units, no further treatment being given

Thus both Haden and Bethell advocate giving 1 cc. of a concentrated extract containing 15 U.S.P. units daily. The former author continues therapy for 14 days, and then twice weekly for 3 months, while the latter continues for a week, and then thrice weekly until the blood is normal.

Our own practice is to give 4 cc. in a single injection of a refined liver extract, such as anahemin, weekly until the clinical and hematologic manifestations of the disease have undergone a complete remission.

Whatever plan of treatment is decided upon, it is, of course, essential that the response to treatment be closely observed during the first two weeks or so, since a failure to elicit an adequate reticulocyte response and rise in the red cell count throws doubt upon the diagnosis or upon the adequacy of treatment

Maintenance Treatment. The importance of adequate maintenance treatment after the restoration of a normal blood level cannot be overemphasized. Failure to appreciate the need of keeping the patient's blood count at normality is undoubtedly the cause of many avoidable cases of irreversible disease of the spinal cord as well as of minor manifestations of ill health.

Since individual patients vary in their requirements for active liver principle, it is impossible to lay down rigid rules for maintenance dosage. In our experience a monthly injection of 4 cc. of a refined liver extract is adequate for most patients, but in some cases larger or more frequent doses may be required, while in others a smaller dosage may be adequate.

An essential feature of proper treatment is the examination of the patient at regular intervals, for only in this way is it possible to ensure that the dosage is adequate Moreover, it must be remembered that the successful treatment of a patient over a long period of time with a given dosage does not justify complacency, since intercurrent infections, the degenerative processes of increasing age, and the possibility of a deterioration of the activity in the liver extracts employed are all factors that may result in failure to maintain complete remission Accordingly, we recommend that when the patient comes for his monthly maintenance dose inquiry should be made for any clinical features suggestive of relapse These include complaints of increasing fatigue, digestive disturbances, sore tongue, parasthesias, or other neurologic manifestations

At intervals of not more than every three months a com[illegible] blood count and examination of a stained film shou[illegible] [illegible] red cell count should not be allo[illegible] [illegible] or 4,500,000 in a female. The [illegible] [illegible]cytic blood picture or of a color index above unity [illegible] also be regarded as an indication for intensified

therapy. The higher concentration of the various members of the vitamin B complex in the cruder types of liver extract has been advanced as a reason for preferring this type of extract to the more highly refined extracts. This suggestion would appear to be dispelled effectively, however, by the widely reported efficacy of the highly refined liver extracts unsupported by vitamin supplements. Moreover, as we have noted on page 508 the vitamin contents of crude extracts is not necessarily higher than that of refined products. Castle believes the administration of vitamins of the B group to be unnecessary and wasteful

Dyke, Della Vida, and Delikat note a tendency of patients with pernicious anemia to relapse during the spring months, and they attribute this to deficiency of vitamin C As the result of therapeutic trials they claim that in certain cases ample dosage of liver extract may be ineffective in securing remission unless it is supplemented with vitamin C concentrates. The evidence presented for this conclusion, however, is criticized by the editors of *The Year Book of General Medicine for 1943.*

Our own experience fails to provide any support for the belief that vitamin supplements are necessary for the treatment of pernicious anemia, provided that a sufficiency of active hematopoietic principle is given and a satisfactory, well-balanced diet is eaten

It must of course be understood that this disparagement of vitamin therapy does not apply to cases suffering from any form of avitaminosis, be it overt or latent Where the history or the clinical examination of the patient points to a vitamin deficiency state appropriate therapy is clearly indicated

Hydrochloric Acid. The fact that gastric achylia is an essential feature of pernicious anemia has naturally led to attempts at replacement therapy with hydrochloric acid It is evident, however, that the quantity of the acid usually given can have little effect on the reaction of a meal in the stomach, owing to the buffer action of the food Koehler and Windsor have shown that 35 cc of U S P hydrochloric acid would be necessary to bring the average meal to less than pH 2, the range necessary for peptic activation The usual dose prescribed (4 to 8 cc), which is as much as the patient can usually tolerate, is therefore ineffective in this respect.

Although the administration of dilute hydrochloric acid with meals may occasionally ameliorate dyspepsia or diarrhea, this measure is generally unnecessary since in the majority of patients these symptoms rapidly disappear with effective antianemic treatment.

Blood Transfusion Reference has already been made to the necessity of transfusing blood in very severe cases of pernicious anemia No dog-

during the period of observation. In 16 of the patients the clinical response was excellent and the average red cell count reached 4,700,000 within 3 months The period before signs of relapse were noted varied from 3 to 10 months. From these observations Askey concluded that a greater storage of liver principle results from the administration of a single large dose of liver extract than from the same amount of active principle given in divided doses.

On the other hand, Seymour, Heinle, and Miller concluded from their studies that if the hematopoietic principle is stored in the body at all, such storage is not quantitative when large doses are administered over a short interval. In general, remissions were shorter with single massive doses than when identical amounts were given in small doses at intervals It is of interest to note that these authors consider that the individual variation shown by patients in their requirements of liver extract depend upon the degree of deficiency of the intrinsic factor and upon the amount of the extrinsic factor taken in their diet. Strauss and Pohle also found treatment at regular intervals to be more effective than with massive doses at long intervals.

These authors made some interesting observations on the time intervals after cessation of treatment before signs of anemia reappeared. The discontinuation of treatment in 15 patients who had previously been maintained adequately for 3 years resulted in the red cell count falling below 4,000,000 per c mm in 2 months in 3 patients, while 3 other patients showed no signs of anemia until after 19, 21, and 27 months, respectively. They conclude that the duration of remission in the absence of treatment is a function of the individual rather than of the treatment. These observations are of considerable practical importance, for not infrequently a patient is encountered who has long been receiving liver treatment, although the original diagnosis of pernicious anemia may be open to doubt. In such a case the diagnosis can often only be decided by withdrawing the liver therapy and watching carefully for signs of relapse. In view of the studies of Strauss and Pohle it is clear that the period of observation would need to extend over 2 years before the original diagnosis of pernicious anemia could safely be rejected

Ancillary Treatment. In the majority of cases of uncomplicated pernicious anemia in the stage of relapse no other treatment than adequate liver therapy is called for beyond a nutritious, well-balanced, readily assimilable diet, and general nursing measures.

Vitamins From time to time claims have been made that the addition of one or another vitamin concentrate exerts an adjuvant effect on liver

is pushed to the point where the patient is symptomatically well and his blood is morphologically normal.

Regarding the prevention of the onset of neurologic complications in patients previously free from them, contemporary opinion is practically unanimous that the maintenance of a normal blood picture by means of adequate liver therapy can confidently be relied upon as an effective prophylactic measure.

In these days when it is exceptional for patients with pernicious anemia to escape recognition for long periods of time, the majority of cases presenting severe neurologic symptoms are met with not so often among untreated patients as among patients who have been receiving inadequate treatment for some considerable time. The occurrence of such cases is therefore largely a grave reflection upon the competence of their medical attendants.

Although the structural changes in the spinal cord are irreversible, the earlier symptoms of subacute combined degeneration may result from functional disturbances of the affected nerve fibers preceding the onset of irreversible disease; hence it follows that considerable symptomatic benefit may result from the institution of energetic liver therapy. As pointed out by Hyland and Farquharson, persistent treatment may produce improvement in at least 50 to 60 per cent of cases, and arrest of further deterioration may be expected in all patients unless infections or other complications interfere with the response to liver therapy. Woltman and Heck claim that 86 per cent of all their patients with neurologic involvement were improved after adequate therapy, although patients whose neurologic symptoms had been present for more than 2 years showed a decreasing prospect of improvement

Strauss, Solomon, and Fox, in their survey of a group of patients treated with parenteral liver extracts for 7 years observed no neurologic symptoms developing in 64 patients who had originally been free from them, while in 21 patients who had shown signs of cord involvement the further development of these manifestations was completely arrested.

In general, it may be stated that symptoms and signs due to peripheral nerve involvement are more amenable to treatment than are others, such as spasticity and ataxia, caused by involvement of the lateral or posterior columns of the spinal cord Symptoms of cord involvement, however, may still be susceptible to considerable amelioration by energetic treatment. Symptoms due to posterior column disease improve more readily than those resulting from lesions of the pyramidal tracts We have observed patients incapacitated with gross ataxia who after intensive liver therapy and remedial exercises were able to walk, dance, and perform work

matic indications for transfusion can be laid down, but its desirability should be considered in cases having a red cell count below 1,000,000 per cubic millimeter. In general the physician must be guided by the patient's clinical condition and the presence of any complicating factor such as infection.

If blood transfusion is decided upon, the danger of overloading the defective circulatory mechanism must ever be borne in mind. The transfusion should accordingly be slow, not exceeding 1,000 cc. in amount, and the patient should be carefully observed for signs of circulatory failure.

Iron. In the later stages of treatment the active red cell regeneration may exhaust the body's supply of iron with a consequent fall in the color index below unity. Under such circumstances medicinal iron should obviously be administered. There is no necessity, however, for giving iron in the earlier stages of treatment in uncomplicated cases, since adequate stores are available in the body.

Treatment of Neurologic Complications. *It is now widely recognized* that the common minor neurologic manifestations of pernicious anemia, such as numbness, tingling, and hyperesthesia, are largely due to peripheral neuritis and generally disappear rapidly and completely with effective treatment.

On the other hand, opinion is still lacking in unanimity concerning the prognosis and most effective treatment of those cases displaying definite signs of involvement of the spinal cord. Of recent years, however, numerous clinical reports have provided substantial support for the view that the essential basis of prevention and treatment is persistent and liberal administration of potent antianemic principle.

As pointed out by Murphy (1939), the published papers dealing with this subject fall into two groups. The first group, containing pessimistic reports on the value of liver therapy in controlling the manifestations of neurologic involvement, was in general based on cases in which the maintenance of a red cell count around the level of 4,000,000 was accepted as evidence of adequate therapy. The second group of papers, which reflects an optimistic attitude, was based on cases which had been treated more energetically, with the object of maintaining the red cell count at 5,000,000 million per cubic millimeter

The position was summed up by Mills who stated that a comparison of results obtained in groups of patients treated with adequate and inadequate amounts of liver extract leaves no doubt as to the efficacy of liver treatment in controlling subacute combined degeneration of the spinal cord, if therapy

extracts is not convincing. We are not aware of any clinical trials with newer preparations such as proteolyzed liver.

It is obvious that the assessment of the relative merits of therapeutic agents in a condition such as subacute combined degeneration can only properly be made after critical clinical trials on a large series of patients over prolonged periods.

In view of the supposed therapeutic effect of thiamin in nerve lesions, many physicians advocate the administration of large doses of vitamin B concentrates as a supplementary form of therapy. Zillhardt, MacLean, and Murphy assessed the effect of this vitamin on the residual neural disturbances in a group of patients who had previously been treated with liver alone They concluded that given in a dosage of 3,000 units intramuscularly, 3 times a week for 2 months, some beneficial effect was occasionally produced Woltman and Heck did not find brewer's yeast to be of value. On the other hand, Bethell concluded that vitamin B given in the form of powdered yeast was of some value in nervous lesions, but its benefit was difficult to evaluate At the present time it cannot be said that convincing evidence is available that the clinical course of subacute combined degeneration is definitely improved by vitamin B therapy.

In conclusion, it may be asserted from a survey of the recent literature and from our own experience that the prevention and treatment of the neurologic complications of pernicious anemia depend essentially upon the administration of the antianemic principle in a dosage fully adequate to maintain a completely normal blood count.

Before leaving this subject, reference may be made to occasional reports of patients displaying the manifestations of subacute combined degeneration of the spinal cord with no history or signs of pernicious anemia. We do not propose to discuss this phenomenon beyond referring to the report of Sanford that improvement may follow liver therapy Cohen described 2 cases in which optic atrophy was believed to be the presenting sign of pernicious anemia before blood or cord changes were present. One of the cases later developed a typical blood picture, while the other had a normal blood count but had achylia and a family history of pernicious anemia In both cases vision improved following liver therapy. We do wish, however, to correct a misapprehension of certain neurologists. We have occasionally been requested to perform a sternal puncture on patients having a normal peripheral blood picture with a view to confirming or refuting a diagnosis of subacute combined degeneration It should, of course, be clearly appreciated that in the presence of a completely normal blood

without obvious disability. In such patients, however, signs of pyramidal involvement such as a bilateral extensor plantar reflex may be unaffected by the treatment.

With regard to the details of the treatment, it may be safely asserted that contemporary opinion is unanimous that the dosage of active antianemic principle should be high It is generally believed that when neurologic manifestations are present the dosage should be at least 2 to 3 times greater than that required to maintain a normal blood count. Thus Dynes and Norcross give 20 U.S.P. units daily for several weeks, followed by the same amount on alternate days for several months, and later at least twice weekly as long as definite improvement continues.

Although the desirability of high dosage in the treatment of neurologic manifestations is beyond dispute, the most effective type of therapeutic substance is still debated. From time to time it has been claimed that the cruder types of liver extract are more effective than the more highly refined ones Although the pathogenesis of the neurologic complications of pernicious anemia is unknown, it is generally believed to be a deficiency state The possibility that the deficient substance may not be identical with the antianemic principle of liver, but that it is some other closely associated substance, provides the theoretic basis for the advocacy of cruder liver preparations

The majority of recent clinical reports, however, provide little support for the alleged superiority of the cruder extracts. Although Haden recommends a cruder form of extract, containing 5 U S P. units per cc., and Strauss, Solomon, and Fox obtained good results with an extract containing 1 unit per cc , neither Evans and Jordan, Woltman and Heck, nor Dynes and Norcross believe that such extracts present any advantage over the more highly refined preparations, while Bethell obtained the highest incidence of good results with concentrated liver extracts. In the absence of any demonstrable inferiority, it is obvious that the more concentrated extracts possess the great advantage of convenience in administration when high dosage is essential

There is little convincing evidence that any form of oral therapy is superior to parenteral liver extracts in the treatment of neurologic disease. In view of the large amounts required, whole liver has the disadvantage of inconvenience in administration. Many of the earlier disappointing results obtained with it were undoubtedly due to inadequate dosage or defective absorption. Advantages have been claimed for hog's stomach preparation by Wilkinson (1933), and by certain Scandinavian writers, but the evidence that this form of treatment is superior to parenteral liver

The treatment of liver sensitivity should be planned according to the severity of the reaction. With patients displaying only mild symptoms it is permissible to attempt to control the reactions by injecting, concurrently with the liver extract, 0 2 cc. of a 1 in 1,000 solution of adrenalin hydrochloride. If this measure is inadequate, satisfactory results may be obtained by reducing the quantity of liver extract to 1/2 or 1/4 of the usual dose, and decreasing the intervals between injections accordingly. Adrenalin may be given at the same time. After a few weeks the normal scheme of dosage may then gradually be resumed.

In the case of patients with severe allergic reactions a choice must be made between abandoning parenteral therapy in favor of some form of oral medication or desensitizing the patient In general, this choice will be influenced by such considerations as the age and general condition of the patient, the question of expense of oral therapy, and the availability of a physician experienced in allergy—for desensitization is an extremely dangerous procedure in inexperienced hands.

We have found the following technic for desensitization to be eminently satisfactory. The degree of sensitivity is assessed roughly by the history of the nature of previous reactions and by the local and general response to an intradermal test injection of 0 05 cc. of the liver extract to be used. If this results in a generalized reaction, desensitization is commenced with a small quantity of liver extract, such as 0 01 cc., but generally 0 05 cc. has been found to be a suitable initial dose. The initial dose is given intradermally The injection is repeated every half hour, the dose doubled on each occasion, and the route is changed to hypodermic when a dose of 0 4 cc. is reached, and to intramuscular at the 1 0 cc. dose. With each injection 0 2 cc of 1 in 1,000 adrenalin hydrochloride is given, the quantity being doubled if any signs of a general reaction develop. If a reaction occurs during the process of desensitization, it usually follows the 1 cc dose. In this event the same dose is repeated in half an hour, and if no reaction occurs the next dose is increased to 1 5 cc and finally to 2 cc. at half-hourly intervals Desensitization is usually accomplished in 3 to 5 hours Before and during the period the patient should drink liberal quantities of orangeade sweetened with glucose Thereafter it is advisable to repeat the final dose of 2 cc daily for 3 days without adrenalin. Weekly doses of 2 cc are now given for 6 weeks and eventually the intervals between the injections may gradually be extended to 2, 3, or 4 weeks. It is most important that the interval periods be only gradually lengthened, and that on no account should they be permitted subsequenty be exceed 4 weeks If this precaution be omitted the patient may again develop sensitivity.

picture, examination of the sternal marrow cannot be expected to provide information of diagnostic significance.

Sensitivity to Liver Extracts. Reference has already been made to the reactions that may follow intravenous injections of liver extract. Such reactions *are usually not due to acquired sensitivity* but are an immediate response of the body to the parenteral injection of foreign material. The adoption of the intramuscular route and improvement in the purification of liver extracts have resulted in their almost complete disappearance.

On the other hand, recent literature provides a number of reports of reactions of an allergic nature occurring in patients who have been receiving intramuscular therapy. *That these reactions are due to acquired sensitivity* is shown by their tendency to appear only after liver therapy has been established for some time, and by the accompanying features of eosinophilia, characteristic skin reactions, bronchospasm, and response to adrenalin. It has also been shown that the sensitivity can be transferred passively by the Prausnitz-Küstner technic (McSorley and Davidson).

A study of the literature *supports our own experience* that these secondary reactions are becoming more frequent. The increasing number of patients receiving parenteral liver therapy provides a ready explanation for this.

The reaction usually occurs within 30 minutes of the injection. Although almost every type of allergic phenomenon may occur, those most commonly seen are flushing, tachycardia, erythema, and urticaria. In severe cases the patient may be seriously embarassed by manifestations such as generalized urticaria, severe bronchospasm, vomiting, rigor, hyperpyrexia, nasal and ocular discharges, substernal pain, angioneurotic edema, lymphadenopathy, uterine hemorrhage, hemiplagia, collapse, and even death (Morgans)

McSorley and Davidson point out that sensitivity to all the leading brands of liver extract has been reported, and apparently as frequently with highly purified extracts as with the cruder ones. Sensitivity may for a time be limited to a particular liver extract, but eventually the patient tends to develop sensitivity to all liver extracts. The claims of Barfred that liver extracts treated with butyl alcohol produced no allergic reactions were not confirmed by McSorley and Davidson.

In a proportion of cases the sensitivity first appears on the resumption of liver therapy following a period during which it has been interrupted. Accordingly, as a measure of prevention, care should be taken to ensure that patients with pernicious anemia receive their injections of liver extract at regular intervals

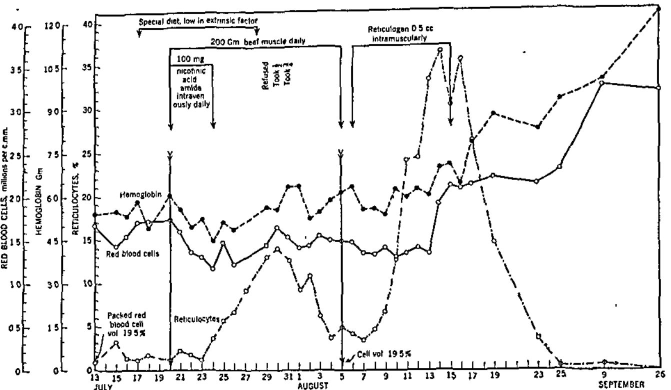


Fig 3. *Submaximal hematologic response* produced by daily administration of 200 grams of beef muscle to a 50 year old male patient with nutritional macrocytic anemia. Graph shows suboptimal response to 200 grams of beef muscle and subsequent optimal response to 0 5 cc. reticulogen. (Courtesy of Moore *et al*, J. Lab. & Clin. Med. 29, 1232, 1944.)

Clinical Treatment of Other Megaloblastic Anemias

Current views on the etiology of the anemias grouped under this heading have already been discussed. The belief that the immediate cause is identical with that of Addisonian pernicious anemia, namely lack of the antianemic principle, would logically require that these anemias be equally responsive to liver or liver extracts. Although broadly speaking this is often the case, in practice the plan of treatment may need to be modified considerably in various respects. The treatment of these anemias will therefore be considered under the several headings previously adopted for their classification.

Nutritional Anemias. As already indicated, this type of anemia, seen most frequently in the tropics but also occasionally in temperate climates, is thought to result from a diet deficient in the extrinsic factor. Recovery might therefore be expected to follow correction of the dietary deficiency. The results of this form of treatment have, however, been variable.

Wills (1933) discovered that the oral administration of autolyzed yeast—marmite—was therapeutically effective in natives of India suffering from this form of anemia. Large doses of 30 grams daily were usually necessary, however; Mudaliar and Menon, on the other hand, reported that autolyzed yeast was ineffective in pregnant Indian women. Trowell (1941) found this substance effective in African natives, but only if given in large amounts which were expensive and difficult to take. Sippe, working in Mauritius, obtained good therapeutic results with the autolyzed yeast product prepared locally, which has already been referred to.

In their study of macrocytic anemia associated with pellagra and other dietary deficiencies occurring in the southern United States, Moore *et al.* found that the daily administration of 200 grams of ground beef muscle resulted in suboptimal reticulocyte responses and eventually in moderate rises in the red cell counts, but that replacement of this therapy by daily intramuscular injections of highly purified liver extracts was usually followed by secondary reticulocyte responses and marked acceleration of red cell regeneration (see Fig. 3). It is of interest to note that, although these patients displayed manifestations of vitamin B complex deficiency, the oral and parenteral administration of nicotinic acid, thiamin, riboflavin, calcium pantothenate, pyridoxine, inositol, *p*-aminobenzoic acid, and choline exerted no hematopoietic effect. This has also been our experience in idiopathic steatorrhea. These authors also produced experimental evidence that the prolonged dietary deficiency may have resulted in inadequate production of the intrinsic factor. This would, of course, provide a plausible explanation for the poor response to therapy based on

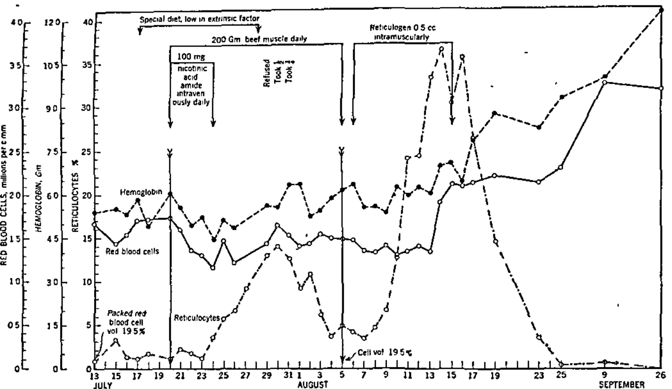


Fig 3 Submaximal hematologic response produced by daily administration of 200 grams of beef muscle to a 50 year old male patient with nutritional macrocytic anemia Graph shows suboptimal response to 200 grams of beef muscle and subsequent optimal response to 0 5 cc reticulogen (Courtesy of Moore *et al*, J. Lab & Clin. Med 29, 1232, 1944)

the administration of the extrinsic factor alone, and would also explain the variable results obtained by other workers According to this view, the response of patients to treatment with food rich in the extrinsic factor would depend upon the degree of impairment of their ability to form the intrinsic factor.

This aspect has been fully discussed by Snapper, whose work on megaloblastic nutritional anemia in China should be studied by all interested in this question.

Parenteral liver therapy in megaloblastic nutritional anemia has been found effective by many observers, but it is generally agreed that the dosage required is often considerably higher than in Addisonian pernicious anemia

The type of liver extract to be preferred, whether crude or refined, has been disputed. Thus, Wills and Evans, Napier *et al* in India, and Trowell (1941) in Africa claimed a superiority for the cruder extracts. On the contrary, Foy and Kondi (1939) in Macedonia, and Mudaliar and Menon in India found crude and highly refined liver extracts to be equally effective The successful results obtained by Moore *et al* in the United States with highly purified liver extracts have already been mentioned

Examination of protocols published by some of the workers mentioned renders it evident that the therapeutic responses tend to be suboptimal and emphasizes the necessity for intensive dosage and prolonged administration

Trowell (1943) has expressed a preference for the oral administration of whole liver when it is available, since it is almost always effective and rectifies other deficiencies in the diet More recently he has drawn attention to the advantages of a new dehydrated liver preparation which was highly effective in doses of 2 ounces daily The dramatic results which we have obtained with proteolyzed liver in the treatment of conditioned nutritional megaloblastic anemia suggest that this preparation is worthy of serious trial in the megaloblastic anemias due to dietary deficiency. Trowell in a personal communication states he has treated successfully 6 cases of nutritional macrocytic anemia in Africa with proteolyzed liver Das Gupta *et al* treated a series of patients in India with proteolyzed liver and obtained satisfactory results Oral administration of proteolyzed liver was stated to be as effective as liver extracts given parenterally

Nutritional megaloblastic anemias are frequently associated with multiple dietary deficiencies, such as lack of protein, vitamins, and minerals. The correction of these deficiencies is necessarily an essential aspect of

treatment. Associated iron deficiency gives rise to the "dimorphic" type of anemia in which the picture may be macrocytic and hypochromic. This clearly calls for the administration of iron in full doses.

In the tropics the clinical picture may be further complicated by infestation with protozoa or helminthic parasites, for the eradication of which appropriate therapeutic measures must be instituted.

Anemia of Pregnancy. Once the diagnosis has been established, by sternal puncture if need be, it is essential that one persist with energetic treatment; with suitable treatment the prognosis is excellent but without it the outcome may be fatal. A variable number of cases respond well to parenteral liver therapy Of 16 cases reported by us (1942, b) 5 showed reticulocyte responses within 4 days of the initial injection. Many cases, however, are temporarily refractory to treatment. Such cases call for persistence with liver therapy and the maintenance of life with blood transfusions when necessary

In the paper just referred to we showed that blood regeneration could eventually be obtained in the refractory cases by repeated injections of liver extract and blood transfusions

Fullerton reported 3 cases of macrocytic anemia of pregnancy and the puerperium which failed to respond satisfactorily to injections of liver extract, both crude and refined, but responded promptly to treatment with whole liver

In more recent studies of our own (Davis and Davidson) we have obtained most gratifying results by treating refractory cases with proteolized liver. The relevant data of a typical case are shown in Figure 4. We have now treated 5 consecutive cases of refractory anemia of pregnancy or puerperium with proteolyzed liver; in each case the response has been prompt and more vigorous than any observed in our earlier series with intensive and prolonged treatment with parenteral liver extract

Once the puerperium is passed and the blood count restored to a normal figure, continuation with liver treatment is usually unnecessary, provided the patient's nutritional status is satisfactory This applies not only to anemias of pregnancy, but to all other megaloblastic anemias in which the fundamental cause for the anemia is no longer operative In purely nutritional anemias, however, a return to faulty dietary habits may result in the recurrence of the anemia (Moore *et al*). In anemias of pregnancy there is, however, a real danger of relapse during subsequent pregnancies The blood condition of patients with a history of anemia during a previous pregnancy should therefore be carefully supervised during later pregnancies.

In older patients the possibility must also be borne in mind of a true

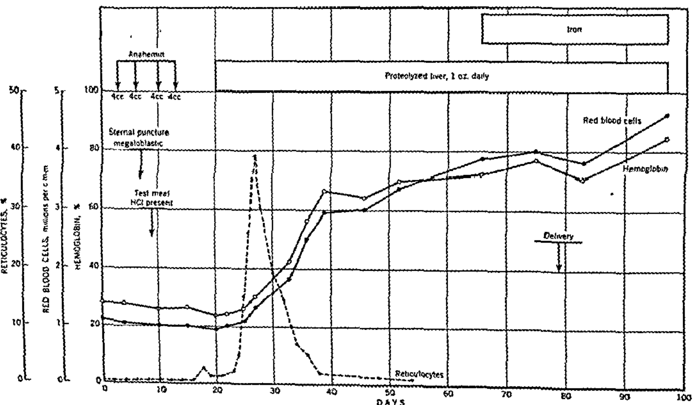


Fig 4 Effect of proteolyzed liver therapy in a refractory case of megaloblastic anemia of pregnancy in a woman aged 26.

Addisonian pernicious anemia occurring coincidentally with pregnancy. In such an event permanent maintenance treatment is of course necessary. Since achylia gastrica may be present in both conditions, the differential diagnosis of megaloblastic anemia of pregnancy from Addisonian pernicious anemia may present great difficulty. Test meals given monthly for 3 months after the puerperium may be of considerable help in doubtful cases, for if the secretion of free hydrochloric acid returns, the diagnosis of Addisonian pernicious anemia may safely be eliminated. Such has been our experience in a number of cases of megaloblastic anemia of pregnancy. If however, the achylia persists, the differential diagnosis can only be made by observing the effect on the blood of cessation of treatment over a period which must extend up to 2 years

Anemias Due to Faulty Absorption. As already indicated, the mechanism underlying this group of anemias is believed to be jejuno-ileac insufficiency leading to a faulty absorption of fat and other substances.

We do not propose to devote space to the larger question of the treatment of steatorrhea in all its manifestations, other than to mention that this is now generally based upon a low fat, high protein diet with liberal vitamin supplements, especially of the vitamin B complex If such treatment results in an amelioration of the general symptoms, especially of the diarrhea, the accompanying anemia, if it be a feature of the case, may undergo spontaneous improvement. However, the majority of cases, which are complicated by macrocytic anemia, require specific antianemic therapy

Since faulty absorption is held to be the cause of the anemia, parenteral therapy would appear to be the method of choice. It is therefore noteworthy that liver extracts in amounts which would produce a dramatic response in Addisonian pernicious anemia may be quite ineffective in cases of steatorrhea with megaloblastic erythropoiesis. Nevertheless, parenteral liver extracts are generally employed for this purpose, although the dosage should be considerably greater than that recommended for Addisonian pernicious anemia A number of writers have claimed that the cruder liver extracts are more effective than the highly refined ones in securing hematologic remission, but in our experience the replacement of the latter type of extract by the former seldom results in a dramatic response, although occasionally it may be followed by a moderate acceleration of blood regeneration

We have recently observed such a result in 2 cases of megaloblastic anemia in soldiers invalided from Burma with steatorrhea They re-

TABLE I

CASES OF IDIOPATHIC REFRACTORY MEGALOBLASTIC ANEMIA, 1941–1945

Age, years	Sex	Initial Hb, %	Color index	Gastric analysis	Duration of symptoms	Refractory period: Duration	Refractory period: Treatment with liver extract, intramuscularly, and vitamins	Response to therapy
13	F.	63	1 23	Free HCl	9 months	Several months	Numerous injections	Slow, to liver extract intramuscularly
20	M	23	1 20	Free HCl	6 months	4 weeks	" "	"
41	F.	22	1 28	Free HCl	18 months	7 weeks	" "	"
34	F.	18	1 20	Achylia	8 months	5 weeks	" "	"
46	M	28	1 19	Achylia	6 months	8 weeks	" "	"
51	F	31	1 19	Achylia	3 years	4 weeks	" "	"
55	F	18	1 16	Achylia	6 months	8 weeks	" "	"
12	F	32	1 42	Free HCl	2 months	3 weeks	16 cc.	Prompt and vigorous, to proteolyzed liver by mouth
21	M	50	1 10	Free HCl	Several years	Several months	Numerous injections	"
47	M.	26	1.45	Free HCl	Over 12 months	Several months	Numerous injections	"
15	M.	44	1 22	Achylia	Several months	2 weeks	4 cc.	"
56	F.	22	1 30	Achylia	2 years	5 weeks	28 cc.	

sponded slowly to campolon although no response had been obtained from numerous injections of anahemin.

Some cases of steatorrhea, and particularly in our experience the idiopathic variety, remain refractory to parenteral liver therapy.

Success has been claimed for whole liver. This has the advantage of supplying valuable protein and vitamins, but may be difficult to obtain and to administer in the requisite quantities over long periods of time to patients whose appetite may be gravely impaired. This latter difficulty may be overcome by the administration of proteolyzed liver. In a proportion of patients with steatorrhea and megaloblastic anemia treated by us with this preparation a satisfactory response was obtained, although potent liver extracts, minerals, and vitamins had all been given previously in large quantities without effect In other cases, however, the results have been disappointing. It is usually possible by diet and hematinics to bring the blood count to approximately 4,000,000 red cells and 80 per cent of hemoglobin, although the rise is slow. However, in some cases continued treatment by every means at our disposal has failed to raise the blood level to normal

Since the essential pathogenesis of sprue and allied conditions is unknown, but may well depend upon a defect in some essential metabolic process such as phosphorylation (Stannus) which in turn may be due to the absence of a coenzyme, the administration of vitamins of the B complex have been recommended

It must be mentioned, however, that in our experience large doses of riboflavin, nicotinic acid, and yeast have failed in many cases of idiopathic steatorrhea to influence materially the blood picture, although features of vitamin deficiency when present were promptly ameliorated The therapeutic effects of folic acid are discussed on pages 541–545.

In conclusion, the treatment of the megaloblastic anemia associated with steatorrhea may be summarized as follows: (*1*) a low fat, high protein diet; (*2*) correction of vitamin and mineral deficiencies; (*3*) administration of large quantities of parenteral liver extract supplemented or replaced in refractory cases by the oral ingestion of whole liver, proteolyzed liver, or folic acid

Idiopathic Refractory Anemias. The treatment of refractory megaloblastic anemias associated with pregnancy and steatorrhea has already been discussed It remains to consider the treatment of refractory cases of unknown origin. As already pointed out these cases constitute a heterogeneous group They may present a clinicopathologic picture identical with Addisonian pernicious anemia, or features such as the presence of

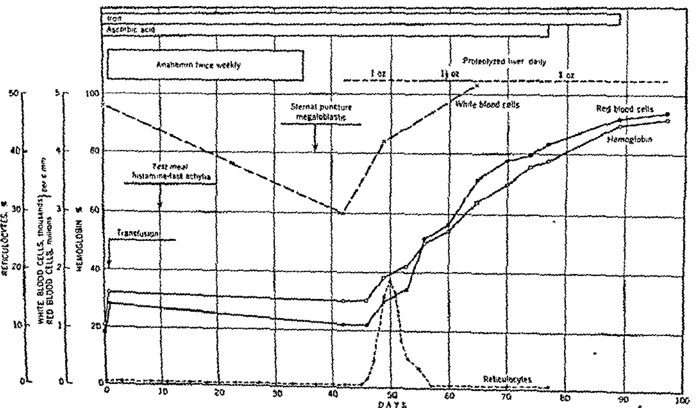


Fig 5 Effect of proteolyzed liver therapy in idiopathic refractory megaloblastic anemia in a woman aged 56.

free hydrochloric acid in the gastric juice, youth of the patient, or defective bodily development may constitute a point of distinction from that condition.

The salient features of the cases seen by us during recent years are shown in the accompanying table (page 536), which also indicates the nature of the treatment employed. It will be seen that in no case have we been unsuccessful in securing eventual hematologic remission. Our earlier cases were treated with repeated injections of liver extract while life was main-

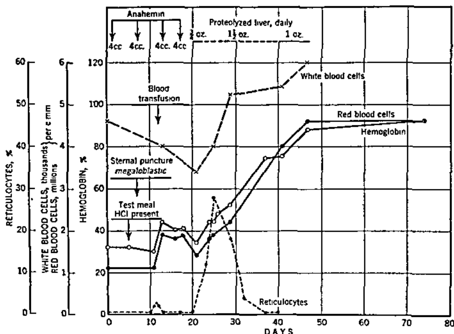


Fig 6 Effect of proteolyzed liver therapy in refractory megaloblastic anemia in a 12 year old girl

tained by blood transfusions, and our later cases with proteolyzed liver administered orally. Although both forms of treatment were attended by recovery, it should be pointed out that they displayed a marked difference in the nature of the response For whereas repeated injections of liver extracts resulted eventually in a slow rise in the red cell count with no significant reticulocyte response, the oral administration of proteolyzed liver was invariably followed by a prompt and rapid reticulocyte and red cell response The hematologic course of representative examples is shown in graphic form in Figures 5 and 6.

In certain of our cases we have evidence that the hematologic remission has been maintained without subsequent treatment for periods of more than 15 months, but as no such case has been under observation for longer than 2 years, we do not wish to draw any conclusions on this point.

Possible explanations for the dramatic responses obtained with proteolyzed liver in refractory megaloblastic anemias have been discussed by us elsewhere (Davis and Davidson) We have suggested that refractory megaloblastic anemias are peculiar in lacking some unknown hematopoietic factor additional to the antianemic principle of Castle, and that efficacy of proteolyzed liver lies in its ability to supply this lack in a readily assimilable form. It is highly probable that this factor is also present in whole liver, which would therefore likely be of equal therapeutic efficacy if taken in adequate amounts We are unaware, however, of any controlled clinical trials to assess the value of whole liver in this connection, apart from Fullerton's experiments in macrocytic anemia of pregnancy.

Fullerton (personal communication) has treated 5 cases of idiopathic refractory megaloblastic anemia with whole liver in doses of $^1/_4$ to $^1/_2$ pound daily with satisfactory results, although all 5 cases had been shown to be refractory to potent preparations of liver extract given parenterally.

In one of our juvenile refractory cases which originally responded to proteolyzed liver, but relapsed on maintenance treatment with intramuscular injections of a so-called "crude" liver extract, a brisk hematologic response followed the administration of an oral liver extract given in doses of 1 5 ounces daily. This observation is of considerable interest in view of similar observations recently published by Watson and Castle on 3 cases of nutritional macrocytic anemia, 2 of which occurred during pregnancy. Liver extracts both crude and refined, given parenterally, were ineffective even in doses of 4 to 5 U S P units daily, but the subsequent administration of oral liver extracts was effective One of the cases which had failed to respond to a specially prepared liver extract given parenterally was successfully treated with the same extract given orally in a daily dose of 10 times the amount which was ineffective when given parenterally Since it is known that liver extract is at least 60 times as active parenterally as when given orally, it was concluded that the therapeutic response to oral therapy could not be explained by dosage Watson and Castle accordingly suggest that in this type of patient the digestive organs may form a new type of hematopoietic substance from the liver extract This theory necessarily conflicts with the unitarian hypothesis which seeks to explain all forms of liver deficiency anemias as a deficiency of the antianemic principle of Addisonian pernicious anemia

Since refractory megaloblastic anemias offer such an excellent prognosis with appropriate treatment, it follows that diagnosis must be firmly established Such cases therefore require a thorough investigation including sternal puncture and the exclusion as far as possible of extraneous factors which might confuse the clinical picture. For it must be remembered that all types of anemia, including Addisonian pernicious anemia, may prove refractory to antianemic treatment if the case be complicated by conditions such as prolonged sepsis, chronic renal disease, myxedema, chronic alimentary disorders, malignant disease, and chronic hemorrhage.

Addendum

Since this article was written, considerable interest has been aroused by reports on the efficacy of folic acid and thymine in the treatment of megaloblastic anemias The following is a brief review of the therapeutic status of these substances, in the light of our present knowledge.

Folic *Acid*

The name folic acid was given to a substance extracted from spinach (by Mitchell *et al.* in 1941) and possessing bacterial growth-promoting properties similar to those of the Lactobacillus casei factor isolated the previous year (by Snell and Peterson) from liver, yeast, and other sources

In 1943, Pfiffner *et al.* obtained from liver a crystalline compound having not only the biologic properties of folic acid but also those of the recently discovered vitamin B_c in promoting growth in the chick. For this and other reasons, the terms folic acid, L casei factor, and vitamin B_c are regarded as synonymous for a substance, or group of related substances whose chemical constitution is as yet unknown.

The possible hematopoietic activity of folic acid was suggested by its effects on rats rendered leukopenic and anemic by administration of sulfaguanidine (Axelrood *et al.*) and on chickens suffering certain dietary deficiencies (Hogan and Parrott, Campbell *et al*)

The difficulties in securing adequate quantities of the pure substance limited its therapeutic trial in man. This obstacle was overcome by its successful synthesis, which was announced but not described, by Angier *et al.* in August, 1945; in May, 1946, the same group described the structure of folic acid and indicated the method of preparation As had previously been suspected, the substance is a pterin derivative. *N*-(4-(2-amino-4-hydroxy-6-pteridyl)methylaminobenzoyl)glutamic acid. Very shortly after the announcement of its synthesis, Spies *et al* (1945) issued a pre-

liminary report on the clinical trial of synthetic folic acid, and a number of additional reports have since appeared.

In their first paper (1945) the Spies group showed that synthetic folic acid exerted significant erythropoietic activity in nutritional macrocytic anemia when given intravenously in daily doses of 20 milligrams or orally in daily doses of 100 to 150 milligrams. In a later paper (Vilter *et al.*) it was shown that the substance was effective not only in nutritional macrocytic anemia but also in patients regarded as cases of Addisonian pernicious anemia. With one exception, good hematologic responses and marked clinical improvement were obtained in each of 4 cases. Treatment was given for periods up to 30 days, and improvement continued after therapy was stopped. Oral administration was more effective than parenteral, although oral dosage was only fivefold that given parenterally. It was noted, however, that the magnitude of the reticulocyte responses and of the increases in red cell counts was not as great as the authors usually obtained in similar cases with large amounts of liver extract, given parenterally. It was also shown that folic acid was without effect in cases of anemia due to iron deficiency, marrow hypoplasia, and myelophthisis.

The results were confirmed by Moore *et al.* (1945), who treated 2 cases of Addisonian pernicious anemia with synthetic folic acid in daily oral doses of 100 milligrams and 30 milligrams, respectively. In each case an early and optimal reticulocyte rise was followed by a satisfactory rise in the red cell count. The same authors also reported the successful treatment of a patient with pernicious anemia of pregnancy by daily intramuscular injection of 20 milligrams of folic acid for 10 days, and of a patient with nontropical sprue who was given 20 milligrams intravenously for 10 days followed by 40 milligrams on alternate days for 14 days.

Doan *et al.* also successfully treated a patient with Addisonian pernicious anemia by intravenous injection of only 2 milligrams of folic acid daily for 20 days. In 3 other patients, who had developed sensitivity to liver extracts, they demonstrated that intravenous injections of 20 milligrams of folic acid were not attended by any manifestations of sensitivity.

In severe megaloblastic anemia in infancy, folic acid was found by Zuelzer and Ogden to be as effective as parenteral liver therapy.

The effect of folic acid in the treatment of macrocytic anemia associated with the sprue syndrome has been recorded in several reports. Thus, Darby and Jones treated 2 cases of nontropical sprue with daily intramuscular injections of 15 milligrams of the substance, in each case a brisk hematopoietic response occurred, together with marked clinical improvement.

Spies *et al.* (1946c) treated 3 cases of tropical sprue in Cuba with 200

milligrams of folic acid daily by mouth, and observed satisfactory hematologic and subjective improvement within 10 days. The same authors (1946d) subsequently reported more fully on a study of 9 patients with tropical sprue. It was found that the response of 3 patients who were given only 10 milligrams daily by mouth was similar to that of the patients receiving 200 milligrams.

Darby *et al.* treated 3 cases of sprue with daily intramuscular injections of 15 milligrams of folic acid, and likewise observed prompt hematologic and clinical improvement.

The experiences of the Spies group with folic acid were summarized by Spies in February, 1946 In all, 45 severely anemic patients had been treated with folic acid, including 8 cases of nutritional macrocytic anemia, 8 of pernicious anemia, 11 of sprue, 3 of pernicious anemia of pregnancy, 1 of carcinoma, 1 of hepatic cirrhosis, 3 of undetermined origin, 3 of aplastic anemia, 3 of leukemia, and 4 of iron deficiency anemia. In patients with megaloblastic erythropiesis, folic acid was highly effective in producing a hematopoietic response. The peak of the reticulocyte response occurred on the 4th to 12th day after commencing therapy. All of the patients experienced marked subjective improvement The dosage ranged from 5 to 400 milligrams daily, and in no case were any toxic effects noted. The optimal dosage has not yet been determined, but Spies suggests that a daily oral or parenteral dose of 20 milligrams should be adequate for an optimal hematopoietic response in most patients

One of us (L S.P.D.) has had the opportunity of observing the therapeutic effect of folic acid* in 10 patients with megaloblastic anemia, 6 of whom were typical examples of classic pernicious anemia in relapse while 4 were cases of megaloblastic anemia refractory to parenteral administration of potent liver extract preparations. A hematopoietic response occurred in all 10 cases and the bone marrow was transformed from the megaloblastic to the normoblastic state The oral dosage in different patients varied from 5 to 20 milligrams daily Only with the 20 milligram dose was the rise in reticulocytes and the increase in erythrocytes during the initial 14 days of treatment up to the standards set up by the U. S P. Anti-Anemia Preparations Advisory Board [illegible]
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mouth responded with a maximal reticulocyte rise and an increase in red cells of 2,000,000 per cubic millimeter in 14 days. Another patient received a single injection of 200 milligrams intramuscularly, with an increase

* Thanks are due to Dr Spies and the Lederle Laboratories, Inc , for the material.

of 1,160,000 red cells in 11 days. No further rise in red cells and hemaglobin occurred in either of these cases after the 14th day. This finding clearly indicates the need for renewed treatment, at weekly or fortnightly intervals.

With regard to the patients suffering from refractory megaloblastic anemia, in 3 cases folic acid alone failed to restore the blood picture to normal. The first was a case of idiopathic steatorrhea; the initial response was excellent, the erythrocytes increasing from 1,370,000 to 3,590,000 in 29 days. Thereafter, continued treatment brought no further hematologic improvement. Parenteral injection of anahemin was also unsuccessful, but proteolyzed liver (1/4 ounce 3 times daily by mouth) produced a further increase of 1,000,000 red cells in 13 days. The second was one of idiopathic refractory megaloblastic anemia. The patient's blood count had fallen steadily, although 24 cc. of anahemin had been given during the month preceding hospital admission. Folic acid transformed the bone marrow from a megaloblastic to a normoblastic state and produced an increase of 750,000 red cells per cubic millimeter in 14 days; continued treatment, however, failed to produce further improvement. Administration of proteolyzed liver by mouth resulted in a further rise of 500,000 red cells. The third case was one of idiopathic refractory megaloblastic anemia which showed a very satisfactory response to folic acid, the red cells increasing from 1,990,000 to 3,850,000 per cubic millimeter in 28 days; continued treatment, however, produced only a slight improvement, and the blood picture still remained macrocytic. A fourth case of idiopathic refractory megaloblastic anemia responded very well to folic acid The red cell count rose from 1.7 million to 4 5 million in 41 days Previous injections of potent liver extracts had produced reticulocyte responses without changes in the blood level.

Of the 4 cases just described, 2 had been under our care previously, both had failed to respond to anahemin, but responded to proteolyzed liver. Is folic acid, therefore, the factor present in proteolyzed liver which is lacking in anahemin? Since it appears that proteolyzed liver may produce a further improvement in the blood level after folic acid has ceased to be effective, one might postulate that there exists in whole liver and in proteolyzed liver some as yet undiscovered hematinic principle additional to the specific antianemic factor present in purified liver extracts and folic acid.

Summary. From the existing evidence, it would appear to be clearly established that folic acid is a highly active hematopoietic agent in many types of megaloblastic anemia Nevertheless, before it can be regarded as a substitute for liver therapy, further information is clearly desirable on the following points.

(1) How effective is folic acid in attaining and maintaining a normal blood picture? Information at present available indicates that it is effective in raising the red cell count to 3,000,000 or 4,000,000 per cubic millimeter. At the moment, however, there are insufficient data published to show whether the blood picture in every case can be entirely restored to normal. Personal communications which we have received from the United States and our own experience clearly show that this result can certainly be obtained in some cases Further information is required concerning such important considerations in maintenance treatment as cost, optimal dosage, and route of administration

In megaloblastic anemia due to the sprue syndrome, it is obviously extremely important to determine whether folic acid will produce a normal blood level, since in so many examples of this syndrome, especially in the nontropical variety, liver therapy is effective in raising the blood count to the 3,000,000 to 4,000,000 level, but is incapable of raising it to normality.

(2) In the reports referred to in this review we have found no reference to the effects of folic acid in megaloblastic anemias refractory to parenteral liver therapy. It remains to be seen, therefore, whether in such conditions folic acid will prove to be as effective as oral treatment with whole liver, proteolyzed liver, or liver extract.

(3) In maintenance therapy of Addisonian pernicious anemia, a vitally important consideration is the efficacy of folic acid in preventing onset of neurologic complications For although folic acid may be effective in maintaining normal erythropoiesis, it may fail to supply the factor, lack of which leads to onset of spinal cord degeneration The inadequacy of folic acid to protect against neurologic complications has been shown by Spies and Stone, and has been confirmed by personal observation in 1 case.

As yet, sufficient evidence is lacking for a definition of the exact biologic relationship of folic acid to the specific antianemic principle in liver. All that can be said at present is that the discovery of the hematopoietic effects of folic acid constitutes an important advance likely to lead to a better understanding of the etiology of the megaloblastic anemias, and possibly to more effective therapy.

Thymine

Spies and his colleagues have recently shown that thymine possesses antianemic properties It is a nucleotide· 5-methyluracil (2,4-dioxo-5-methylpyrimidine), which was isolated and synthesized many years ago Stokstad showed it to be capable of replacing folic acid as a growth factor

for lactic acid bacilli. Bacteria thus grown with thymine are devoid of folic acid and require about 5,000 times as much thymine as folic acid (Stokes). It was accordingly suggested that folic acid may act as an enzyme or coenzyme in the synthesis of thymine or thyminelike compounds which are utilized in the production of nucleic acid, thus forming an integral part of the biologic cell

Spies *et al.* (1946b) studied its effect in a case diagnosed as Addisonian pernicious anemia. Given in daily oral doses of 1 gram it was without effect, but increasing the daily dose to 6 grams resulted in a significant erythropoietic response; 2 other patients given daily 10 2 and 4.5 grams by mouth, respectively, also showed satisfactory responses. Apparently treatment was not continued for more than 14 days, and the recorded observations covered only 3 weeks; the nature of the subsequent response, therefore, is not stated.

In a later paper, Spies *et al.* (1946a) described the effect of a daily dosage of 15 grams of thymine by mouth in 4 cases of tropical sprue in a state of hematologic relapse Prompt hematologic and clinical improvement followed in all 4 cases, although the clinical response was reported as less dramatic than that observed with folic acid. Here again, however, the period of treatment and observation did not exceed a month, and the highest red cell count attained was in the region of 3,500,000.

Although these studies have clearly demonstrated that thymine possesses a significant hematopoietic effect, it remains to be seen whether it is equal or superior to that of liver preparations in various types of megaloblastic anemia If, as appears to be the case, thymine is no more effective than folic acid, the fact that the dosage of thymine is approximately 1,000 times greater suggests that this substance may be of little therapeutic importance. A decision, however, must be delayed until additional information, particularly as to cost and ease of manufacture, is available.

Choline

Moosnick *et al* have described successful treatment of a case of refractory megaloblastic anemia with intravenous injections of choline chloride in doses of 1 gram Recent trials by one of us (L J D) in 8 cases of different types of megaloblastic anemia have been disappointing. Given either orally or intravenously in daily doses as high as 10 grams, choline chloride produce a suboptimal hematopoietic response in only 3 cases. It does not therefore seem that this substance will be of much practical value in the treatment of megaloblastic anemias.

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substances are larger than normal, or in which there is decreased absorption, increased excretion, or impaired assimilation or utilization of some of the dietary substances In such cases a negative balance can be avoided only by providing for the increased requirements Prevention of this type of malnutrition requires knowledge of the kinds of nutritional disturbance and the corresponding demands in various diseases, and of methods of increasing intake and decreasing loss or consumption of the necessary nutrients Still another type of nutritional deficiency is actually due to the metabolic inability of the body cells to assimilate the required food elements Such deficiencies are fortunately rare, but they cannot be prevented, at least by any procedure known at present

In one type of metabolic disturbance the assimilation of protein is sometimes impaired. In otherwise healthy individuals during certain "catabolic phases," as after injury and infection, protein cannot be utilized (1,12,21), for reasons which seem mysterious at present but may be clarified in the future. Some believe such loss necessary and inevitable, and that no attempt should be made to compensate for it until the disease is past this stage of obligatory negative nitrogen balance. Obviously, prevention is better than cure. If tissue wastage, malnutrition, and deficiencies are deleterious, it is better to preclude than to correct them. Modern medicine aims to prevent deficiencies by providing food at all times so that the body may use it as soon as possible. Considerable evidence has shown that after operations at least, even when nutrition is limited to the parenteral route, much of the nitrogen loss may be avoided (2,5).

The Six Essential Nutrients

A complete diet comprises six different groups of substances, all of which must be included in order to attain a good nutritional balance. Most of these groups are subdivided on the basis of the identification and purification of their basic units. These relatively simple chemical substances are prepared by the body itself from food in the gastrointestinal tract before absorption into the blood stream. In Table 1 the six nutritional groups are given, with the basic units derived from them in the gastrointestinal tract.

Functions of the Six Nutrients. Adequate performance by the various nutrients is necessary to the anatomic integrity and physiologic efficiency of the body. They must therefore not only be supplied and absorbed in proper quantity, but definite relationships must be maintained between them to ensure an optimum state of the cells and tissues. For

Nutritional Requirements in Disease*

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Introduction

It is now recognized that a knowledge of nutrition is a prerequisite for the treatment of disease. However, the education of medical students as well as of graduate physicians has not kept pace with the tremendously increased amount of information which the great advances in the science of nutrition have made available It is time to discard empiric practices or the unfortunately common laissez-faire attitude toward food requirements in disease and to employ in their stead, so far as possible, preventive and therapeutic measures based upon fact

Definitions As a preliminary to our discussion of the nutrition of patients, a few terms need definition·

(*1*) Malnutrition implies the existence of nutritional deficiencies due to a disparity between intake and utilization or expenditure of the various dietary elements. The two terms, malnutrition and nutritional deficiency, may be considered as synonymous.

(*2*) The term "in balance" denotes a food intake which equals output. Thus, for example, a patient in balance shows energy balance (total calories), water balance, electrolyte balance, nitrogen (i.e., protein) balance.

(*3*) A positive balance signifies retention and storage of nutrients, while a negative balance indicates a net loss. The balances for the various nutrients may operate more or less independently so that total caloric balance may be positive while calcium or protein balance may be negative.

(*4*) Starvation means, merely the deprivation of one or more necessary elements in the diet, either in part or completely.

Types of Malnutrition Inadequate intake or absorption of food combined with normal expenditure inevitably produces a negative balance and leads to malnutrition But malnutrition may occur with a normal dietary intake, as in disease conditions in which the requirements for certain food

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protein. Fats are expensive to produce; during times of famine or war fat is apt to be the most seriously curtailed of all nutrients. In Madrid, in 1941, fat furnished only about 10 per cent of the calories of the average diet, and in 1942 Belgium and Finland were restricted to only about a fifth of their prewar fat consumption (3).

Proteins. These constitute about 75 per cent of the dry weight of the body tissues. Proteins are most important as structural material, and in the plasma and red cells contribute to the essential properties of blood. Proteins are also necessary for the formation of enzymes and hormones, and thus also furnish catalytic substances and chemical regulators. Protein materials, therefore, together with the minerals constitute the metabolic machinery of the body. Of all the food essentials, protein is probably closest to the vital processes; its very meaning is derived from the Greek root meaning *primary* or *first.*

Proteins supplied in excess of structural needs are converted into fuel. When caloric intake is inadequate, stored fat is used first; carbohydrate stores are then used, but being relatively scant, are quickly exhausted. In such circumstances body protein will then be used for fuel. Lusk (15) has estimated that, under conditions of complete starvation, 87 per cent of the calories will come from adipose tissue and 13 per cent from protein tissue. To maintain normal function the daily protein intake is usually set at 1 gram per kilogram of body weight, 1.5 grams probably being nearer the optimum level; this means 105 grams a day for a 70 kilogram (154 pound) man.

Water. Water furnishes the vehicle for absorption of nutrients into the body, constitutes the chief ingredient of the extracellular fluid, provides for excretion and secretion, and by evaporation from lungs and skin is responsible for about 25 per cent of body heat loss, thus contributing to temperature regulation When water intake is undisturbed, little attention to the intake is usually necessary Excesses of water are easily disposed of unless some factor, such as circulatory failure, nephritis, or hypoproteinemia, interferes with excretion Water enters the body per se, as a constituent of other foods, both liquid and "solid" (which are often actually 70 to 80 per cent water), and as water of oxidation The exact water needs vary greatly with the temperature of the environment, with bodily exertion and heat production, and with salt intake Under extreme conditions the need for water may be as high as 10 liters per day; the minimum requirements of an average normal man in a temperature environment are 1 5 to 3 liters per day.

Vitamins Their functions are important, but lack of them is usually

TABLE I

THE SIX NUTRITIONAL GROUPS AND THEIR BASIC UNITS

Nutritional group	Basic units
Water	Water
Salts and minerals	Sodium, and potassium chloride, calcium, phosphorus, iron, etc.
Carbohydrate	Glucose (dextrose)
Fat	Fatty acids
Protein	Amino acids and small peptides
Vitamins	Vitamin A, thiamin, riboflavin, nicotinic acid, ascorbic acid, vitamin D, etc.

example, an increase in the salt intake requires a proportionately greater supply of water so as to keep the electrolyte composition of the extracellular fluid within normal limits. Likewise, an increase in the carbohydrate combustion demands an increase in the available thiamin

The nutrient elements may be classified according to three general functions (17): (*1*) as structural or supportive material (bone, cartilage, skin, connective tissue, stroma of individual organs, and cells; and the blood plasma, interstitial fluid, and lymph, which together constitute the medium of transport, the extracellular fluid); (*2*) as fuel (for body heat, muscular activity, and work, as well as for the energy for numerous complex intermediate metabolic processes); and (*3*) as catalytic substances, or chemical regulators

The function of each of the nutrient elements is not a single attribute, for every essential nutrient falls into more than one of the three categories For example, by far the chief function of carbohydrate is to supply fuel, but some is used in the construction of special conjugated proteins in cartilage, and some is needed in the formation of certain enzymes Fats are used primarily for fuel They also serve largely as fuel storage materials; adipose tissue furnishes some structural support, and the fatty substances known as phospholipids and cerebrosides are important constituents of tissues and organs. Furthermore, fats supply the essential fatty acids (linoleic and arachidonic), carry the fat-soluble vitamins A, D, E, and K, and facilitate the absorption of calcium and phosphorus

Carbohydrate and Fat Together, they supply about 90 per cent of the calories in the average normal diet In the poorer types of diets, used especially in the lower economic groups, about 60 to 70 per cent are supplied by carbohydrate, 20 to 25 per cent by fat, and about 5 per cent by protein In better diets, about 50 per cent of the total calories are derived from carbohydrate, 35 or 40 per cent from fat, and 10 per cent or more from

regard to the intake of foods containing many of the vitamins, which include such items as whole wheat products, fresh fruits, and vegetables, will give the physician a fairly good indication of the probable existence of vitamin deficiencies. Protein and vitamins are the elements in which diets are most often deficient Most persons ingest sufficient carbohydrate, fat, and minerals (with the possible exception of calcium and iron). Thinness alone suggests simply lack of calories, but nutritional deficiencies may be suspected in the presence of certain anatomic or physiologic abnormalities, such as neuritis, dermatitis, or bleeding gums. Although various tests can be carried out to verify suspicions, in most cases the evidence is presumptive and is based largely on a nutritional history which reveals inadequacies.

Second, there are the problems presented by specific deficiency diseases, mild, moderate or of the full-blown, classic type. Most of these diseases are caused by inadequate intake of various vitamins (e g., xerophthalmia, beriberi, pellagra, scurvy, rickets), but in many instances disorders follow an inadequate intake of protein (e g., hypoproteinemia, edema, anemia). There is no need to discuss the clinical manifestations of this group of diseases here since they are adequately treated elsewhere, and information on typical specific nutritional diseases is rather widely available

The third way in which nutrition and disease are related is through the effect of disease itself in lowering the nutritional status of the patient and the reciprocal influence of the resulting malnutrition upon the course of the disease. It has become increasingly evident that even when at onset the patient is a normal, well-nourished individual, malnutrition of one type or another develops, sometimes rapidly, during the course of most diseases. Too often in the past physicians have viewed such malnutrition with complacency. Indeed, malnutrition was even considered an inevitable accompaniment of disease, so that little attention was paid to this problem and this type of malnutrition was insufficiently studied Few measures were taken to prevent it, and only when the process had produced severe wasting were therapeutic attempts made to restore the nutritional status

Starvation and Anorexia. In view of this traditional attitude, two questions may be asked. First, is starvation harmful? The answer to this question is an unequivocal *yes.* If food is necessary for life during health, it seems obvious that it is even more necessary during the stress of illness, since hardly ever is the average patient unable to utilize nutrient essentials by one or another channel A possible exception is the patient who may be unable to utilize protein or perhaps calcium during "catabolic periods" There is no justification for starving the injured or sick organism which

not evident until deprivation has been prolonged, since vitamin stores are only gradually exhausted. However, if treatment is to be most effective, vitamin deficiencies should be detected early, before florid signs appear. Four successive stages of avitaminosis may be distinguished: (*1*) tissue depletion, (*2*) biochemical disturbances, (*3*) functional changes, and (*4*) anatomic lesions.

Normal Nutritional Requirements. These are fairly well known, not only in terms of the six nutritional groups, but in terms of the actual natural food materials as they are consumed, each of which, of course, contains varying proportions of the six nutritional substances. Table II lists the approximate requirements of the six nutritional substances when the energy expenditure is about 2,500 calories per day.

TABLE II

NORMAL NUTRITIONAL REQUIREMENTS FOR AN ENERGY EXPENDITURE OF 2,500 CALORIES PER DAY

Substance	Quantity
Water	3,000 cc.
Electrolyte (salts of Na, K, Mg, etc.)	10 Gm.
Ca, 0.8 Gm.; Fe, 12 mg.; etc.	1 Gm.
Carbohydrate	300 Gm.
Fat	120 Gm.
Protein	70 Gm.
Vitamins (vitamin A, 5,000 units; thiamin, 2 mg.; riboflavin, 3 mg.; nicotinic acid, 20 mg.; ascorbic acid, 75 mg.; vitamin D, 500 units)	100 mg.

Relation of Nutrition to Disease

Nutrition and disease are related to each other in three general ways. The first is the nutritional state of a patient before the onset of the illness; obviously, the existence of specific or general malnutrition in a person who falls sick will influence the course of the disease, whether medical or surgical in nature, acute or chronic. The physician must recognize this, for the pre-existing malnutrition must be treated as well as the disease itself. The fact that the patient is underweight or has been losing weight is particularly suggestive. In most instances a simple history of the patient's dietary habits will reveal the probable presence of nutritional deficiencies. Information on the number of eggs eaten, the frequency of meat in the diet, and the amount of milk or other dairy products such as cheese usually included will show the probable adequacy of the protein intake, while inquiry with

only result and little if any physiologic impairment follows. If the deficiency concerns not only calories but perhaps protein and certain minerals or vitamins, other much more important evidences of the nutritional disturbance eventually appear. The clinical effects of such malnutrition, however, are often masked during a long developmental period. The term "subclinical" is often applied to this period of malnutrition, corresponding to the phases of tissue depletion and biochemical disturbance. The manifestations are vague and nonspecific, and include anorexia, general malaise, asthenia, lack of endurance, and fatigability. Many of the symptoms are referable to vitamin deficiencies. In general, however, it is difficult to make a definite diagnosis of malnutrition on such subjective manifestations

The chemical manifestations of malnutrition can be used in the diagnosis of some conditions. Thus, the presence or absence of some of the vitamins, notably vitamins A and C, in the blood and urine, can be established quite easily, while that of others can be ascertained only with great difficulty or not at all The electrolyte concentration in the blood, particularly that of chlorides, is easy to measure Serum concentration of proteins can be readily estimated and may be of considerable value, particularly when the albumin fraction is determined. Clinically, the commonest nutritional defect is probably a negative caloric balance with weight loss. Perhaps next in frequency are dehydration and electrolyte disturbances, then vitamin deficiencies. Depletion of protein, although often overlooked, produces important and not uncommon clinical manifestations.

Loss of Weight. A fall in the total body weight is frequently a sign of malnutrition, but not invariably so In the first place, loss of weight is of serious physiologic significance only when it signifies loss of protein tissue Loss of adipose tissue produces no deleterious effects; indeed, in the obese it may improve physiologic performance. For this reason loss of weight in itself may not be significant as a manifestation of malnutrition On the other hand, a person may suffer definite malnutrition without loss of weight whenever an excess of adipose tissue masks protein, mineral, or vitamin deficiencies

A disturbed water balance also influences body weight. Dehydration causes rapid weight loss, edema produces rapid weight gain. Protein loss may be associated with weight gain, particularly in extreme malnutrition, with hypoproteinemia, and edema The retention of water may be evi- [illegible]

tion may first cause weight loss but later, with the occurrence of water

needs at least normal amounts of the essential nutrients known to be required for normal function

The second question is really a corollary of the first: Can the physician safely rely on the patient's appetite to determine the body's needs and thus the dietary intake during illness? Appetite, even in healthy individuals, is a variable matter. In the sick its vagaries are well known; *dependence upon the patient's desire for food during illness or after injury or operation almost always means a certain degree of starvation.* If starvation is harmful, the answer to the question therefore must be *no*; appetite, in other words, is not a reliable guide Anorexia, a frequent accompaniment of most diseases, must therefore be combated along with other clinical manifestations. If food is necessary in disease, anorexia cannot be accepted as an inevitable symptom; the therapist must accept it as a challenge rather than as a justifiable excuse for starvation.

Anorexia is only one of the factors which may interfere with the ingestion of food *It is common after operations, anesthesia, visceral pain, as well as in such conditions as alcoholism, congestive heart failure, fever and infections,* and thiamin deficiency Failure to consume the proper quantities or varieties of food may be a matter merely of poor choice, or lack of appetite in illness, on the other hand, it may be due to neither of these factors Other factors which prevent adequate intake of a balanced diet include: psychiatric conditions, neurologic and gastrointestinal disorders, loss of teeth, sore tongue and mouth, pregnancy, and so-called therapeutic diets in which essential nutrients are excluded, as for example eggs because of allergy, or citrus fruits because of peptic ulcer.

Clinical Effects of Malnutrition

Malnutrition is obvious when it is in an advanced stage, but in the beginning it is barely evident (13). Yet its presence should always be suspected whenever there has been a negative nutritional balance In other words, the existence of nutritional deficiencies must be assumed in any patient in whom the loss or consumption of one or more essential nutrients has exceeded the intake The most acute and dramatic disturbances result when the negative balance of electrolyte and water is of serious proportions, when not only intake ceases, but there are large losses as well through vomiting, diarrhea, or blood loss Weight loss develops quickly with water deficiency; weight loss also soon becomes evident when the total caloric intake is inadequate and the body must use its own tissues If inadequate intake is limited to calories and is of short duration, loss of stored body fat is the

ure to absorb vitamin K in obstructive jaundice, or due to liver disease and inability to make prothrombin may cause serious bleeding.

(3) Protein deficiency may cause serious clinical manifestations usually related to the development of hypoproteinemia. The nutritional edema which may result, either occult or clinically evident when it involves subcutaneous tissues, is responsible for such phenomena as delay in wound healing and renal impairment, and may even be associated with circulatory failure It probably also affects the gastrointestinal mucosa, impairing the functions of motility, digestion, and absorption, and even leading to manifestations suggestive of intestinal obstruction

Hypoproteinemia is often found in patients with severe protein deficiencies; since it can be detected by chemical measurements, it offers a useful means of clinical diagnosis. Unfortunately, hypoproteinemia may be masked; for example, the plasma protein concentration may be normal while the total amount of circulating blood protein is decreased. This is the result of hemoconcentration due to dehydration of one type or another. As ordinarily encountered in a malnourished individual, the initial measurement of the serum protein on entrance to the hospital is normal, but as dehydration is corrected the value falls and subsequent measurements reveal the true state of affairs Simultaneous hematocrit measurement or red cell count is a useful way of detecting such changes in plasma volume and it should always be carried out along with measurements of serum proteins

A high concentration of serum globulin may also mask the presence of hypoproteinemia Nutritional hypoproteinemia is reflected by a low albumin fraction of the plasma If there is a simultaneous increase in the globulin fraction, measurement of total proteins will reveal a deceptively normal value. For this reason fractionation of the serum protein, i.e., determination of the albumin and globulin fractions, is the only way of detecting this type of hypoproteinemia Indeed, the term "hypoalbuminemia" is a much more accurate designation than the less specific "hypoproteinemia" Liver disease may also be associated with an increased globulin concentration and thus mask the existence of a hypoalbuminemia if total proteins alone are measured (9).

(4) Lowered resistance to infection is a serious sequel of malnutrition. Many types of infection, particularly pneumonia and tuberculosis, have been known to follow in the wake of famine The malnourished individual is not only less able to resist the invasion of a serious infection, he may even be unable to overcome mild infections which normally cause very little difficulty. The reason for this lowered resistance to infection has been

retention, the body weight may return to or exceed that which is normal for the individual.

This influence of body water upon body weight often leads to a curious paradox. Patients improving on an adequate protein intake will lose weight for a time due to diuresis before they start to regain their lost tissue. Conversely, a patient on an inadequate protein intake may gain weight due to an increasing retention of water.

Mild Clinical Manifestations. Malnutrition produces symptoms of weakness or asthenia which may be difficult to appraise accurately. Hunger may disappear within a few days during malnutrition and may be replaced by anorexia Postoperative manifestations of weakness and asthenia have often been attributed to the operative procedure itself, as inevitable results of discomfort and confinement. Recent study, however, has shown that many of the symptoms may actually be due to starvation, particularly to deprivation of protein (18,24) An excellent study of the effect of feeding on postoperative asthenia is the one made by Mulholland *et al.* (19). They showed that when jejunal alimentation was begun immediately after gastric resection many of the usual postoperative symptoms were alleviated and convalescence accelerated.

Mild manifestations of vitamin deficiencies have been described by a number of observers These include such symptoms as nervous irritability, asthenia, anorexia, and even nausea and vomiting. Tissue depletion of protein or of vitamins may be advanced before symptoms develop Weight loss, when accompanied by fatigue, irritability, headache, insomnia, and depression, is especially suggestive

Serious Clinical Manifestations. These include a variety of signs and symptoms

(*1*) Serious clinical manifestations due to dehydration and salt loss are fairly well known and need not be described here.

(*2*) Severe specific avitaminoses are well known and will not be further described. Classic beriberi, pellagra, rickets, or scurvy, are not encountered frequently, although less severe degrees of specific vitamin deficiencies are common. For example, Pollack, Ellenberg, and Dolger (22) daily visited a surgical ward of 38 beds for a whole month and during this period found 9 patients in whom a diagnosis of vitamin deficiency could be made The two vitamins involved were nicotinic acid and riboflavin. All responded to specific therapy, and in 1 case the patient's life was saved In a study of 200 patients in the Charity Hospital of New Orleans by Goldsmith (10), 40 per cent were found to exhibit signs suggestive of riboflavin or nicotinic acid deficiency, or both. Hypoprothrombinemia due to fail-

ure to absorb vitamin K in obstructive jaundice, or due to liver disease and inability to make prothrombin may cause serious bleeding.

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investigated by Cannon (4) and his co-workers They have shown that antibody production is greatly impaired whenever the diet contains little or no protein. It seems, therefore, that the immunologic failure during malnutrition can be correlated with a protein deficiency.

(*5*) Mineral depletion may result from prolonged, normal losses without adequate replacement. Such depletion may ultimately interfere with the structural and physiologic functions of these important nutrient elements. *Accelerated losses or inadequate intake may rapidly bring on* the resultant deleterious effects. Inadequate intake of calcium (or phosphorus) and of vitamin D, or losses due to pregnancy, lactation, immobilization (as in casts), hyperthyroidism or hyperparathyroidism, impaired bile secretion, or chronic diarrhea may lead to osteoporosis and possible vertebral collapse or pathologic fractures. Hypocalcemia with tetany may in rare instances be caused by calcium depletion or avitaminosis D. Iron deficiency with resultant hypochromic anemia may result from an insufficient supply of this mineral during the growth period, or from a drain on the iron stores by pregnancy, lactation, menstruation, or hemorrhage (acute or chronic)

(*6*) Impaired hepatic function has been shown to follow malnutrition The influence of carbohydrate depletion on hepatic function has long been known, but it has now been shown that deficiency of choline in the presence of a high fat–low protein diet will also produce hepatic damage. Furthermore, recent experimental evidence (11) indicates that hepatic injury (cirrhosis) results from insufficient protein intake in association with lack of some unidentified vitamin B factor. Experiments (8) in which hypoalbuminemia was produced in dogs by dietary means showed a decrease in liver protein content and impairment of liver function.

(*7*) The final and tragic manifestation of severe malnutrition is death. Not uncommonly patients with one type of disease or another become severely malnourished and finally die without malnutrition being considered as an important cause of the fatal outcome But many postmortem examinations show lesions that have either healed or are insufficient to account for the fatal outcome Inasmuch as death is an *inevitable result of starvation* in normal individuals, it is not surprising that those suffering from some injury or disease also may die because of an inadequate intake of food

Increased Nutritional Requirements during Disease

Nutritional requirements are considerably increased in various types of disease. The requirements will be mentioned under the separate headings of the various nutritional elements.

Water and Electrolytes. Water and electrolyte requirements are considered together because they are intimately connected metabolically. Requirements for these two basic units are increased in any disease in which there is excessive loss. The most common conditions are fairly well known and involve the loss of gastrointestinal secretions by vomiting, diarrhea, or through intestinal fistulas Closely allied to this type of water and electrolyte loss is excessive sweating caused by increased environmental temperature or by fever. In diabetes mellitus, water and salt loss may be chronic and mild (when dehydration is moderate); or acute and severe (when dehydration is extreme, as in diabetic acidosis or coma).

The amount of water and electrolytes which may be lost in a few hours or in a day under these conditions may reach the equivalent of several liters of isotonic saline solution. The loss, for example, may amount to 4 liters or more of water, containing 36 grams or more of sodium chloride The physician should be able to recognize from the history alone the existence if not the degree of such losses He should promptly be impressed, therefore, by the need for replacement Patients seldom know exactly how much fluid they have lost by vomiting or diarrhea, but the mere presence of these symptoms immediately suggests the need for meeting such losses. Not only replacement but correction of the cause of a gastrointestinal upset, or in diabetes, the correction of the metabolic status, with abolition of the glycosuria and ketosis or acidosis, is necessary to relieve permanently the salt and water deficit.

The term "dehydration" is often applied to the results of such loss of water and electrolytes and this term is an accurate one, provided its variations are understood Dehydration really means loss of water; the variations arise from the substances which accompany this water loss. In the type just described, the water loss involves loss of salt in approximately isotonic concentration, i e , the loss of 9 grams of salt for every liter of water. In other types of dehydration, as for example that following extensive burns, pneumonia, peritonitis, or intestinal obstruction, the water which is lost contains not only electrolytes but also protein Because the protein concentration in the fluid lost approaches that of plasma, this type of dehydration may be called plasma dehydration and will be discussed under protein requirements

Dehydration may involve loss of water alone, with very little loss of electrolytes, this occurs in starvation when there is no water intake. Water is essential for the vital processes and will be obtained from body stores as long as life lasts; when no water is ingested, the various body tissues become drier and drier, extracellular water being lost first, then cellular water,

until death occurs. The significant difference between this type of dehydration and that which follows vomiting or diarrhea is the failure to lose electrolytes. Indeed, the concentration of solids in the body grows greater, its osmotic pressure increases, and death ultimately results from the accumulation of these substances in the body. That is why the administration of pure water in starvation will prolong life considerably. From the practical point of view, water administered in this type of dehydration must contain relatively little electrolyte in order to avoid further increase in the osmotic pressure of the body fluids. Instead of isotonic saline solution, a glucose solution should be given, containing perhaps only 2 grams of sodium chloride per liter rather than 9 grams per liter. This small amount of salt is necessary because there is a slight loss of salt during early water deprivation Although lack of water is a basic cause for this simplest type of dehydration, insensible loss through the skin under conditions of high environmental temperature will accelerate the progress of dehydration due primarily to lack of intake

Energy Needs. True increased requirements for calories in disease (not due to inadequate absorption or excessive excretion of nutrients) occur in hyperthyroid states, in fever, and in cancer and other neoplastic diseases. A patient at rest in bed ordinarily requires no more than 10 to 15 calories per pound of body weight (approximately 25 to 30 calories per kilogram), or about 2,000 calories for an average-sized individual In fever the need for calories increases at a rate of about 7 per cent per Fahrenheit degree Fever, in addition, is often accompanied by destructive processes which break down body tissue and cause excessive urinary elimination of structural elements, such as calcium and phosphorus in osteomyelitis or nitrogen in cancer In hyperthyroidism, the increase in caloric requirements is the result of (*a*) an accelerated basal metabolism, plus (*b*) an increment caused by the purposeless hyperkinesia so common in the disease, plus (*c*) an inefficiency of motor activity which requires greater than normal energy expenditure for normal purposeful motion. Thus, a patient suffering from thyrotoxicosis and having a basal metabolic rate of +50 per cent requires more than an *increase of 50 per cent in his caloric intake to maintain* a normal energy balance and to prevent weight loss The caloric requirements of a 35 year old thyrotoxic man, 67 inches tall, weighing 154 pounds, who spends 16 hours daily in bed or chair and 8 hours in sleep may be calculated (approximately) as shown in the table on the next page.

Since patients with hyperthyroidism usually have lost weight, they should be given food in excess of their exact needs; from 4,000 to 5,000 calories daily is often indicated Intake should be sufficient to permit stor-

[illegible]

	3,039
Plus 10 per cent for specific dynamic action of food	304
Total.	3,343

age of protein, fat, carbohydrate, calcium, and other essential nutrients of which these patients have been depleted

Such physiologic conditions as pregnancy, lactation, and prolonged and repeated strenuous exertion raise specific mineral and vitamin demands, as well as caloric requirements. Abnormally high environmental temperatures imposed by climate or industry may raise the requirement for all nutrients. Psychologic conditions, if maniacal in type and accompanied by delirium and by hyperactivity, may also increase the total metabolic needs

Protein Needs. Assuming that the protein is of good biologic value, the normal individual requires about half a gram of protein per pound of body weight to maintain nitrogen balance (1 gram per kilogram), but in certain types of disease the needs are increased tremendously. These may be divided into two groups, according to whether the loss is actual or metabolic. The actual increased protein needs result from a direct loss of protein from the body in one or more ways These are: (*a*) loss of hemoglobin and plasma protein in hemorrhage; (*b*) loss of plasma protein as such in the urine or from the surface of burns and wounds, (*c*) loss of plasma protein into the body cavities (peritonitis, empyema); (*d*) loss of plasma protein into tissue (e g , in burns, pneumonia, intestinal obstruction, tissue trauma). Metabolic loss of protein occurs when there is excessive destruction of tissue protein. This is often called "toxic destruction," and occurs in the following conditions. (*a*) after operation or injury, or as part of the so-called "alarm" reaction, (*b*) infections of various kinds; (*c*) so-called toxic states which may follow infections long after the existence of fever and other evidence of infection have subsided; (*d*) immobilization or bed rest

The amount of protein lost may be tremendous In terms of actual loss, as much as 50 grams a day may escape from the surface of burns and other wounds. In a single hemorrhage with the loss of 1 liter of blood, 150 grams of hemoglobin and 50 grams of plasma protein are lost. When the losses are metabolic, the amount may reach larger proportions. In a case of

pneumonia, for example, the daily loss of nitrogen may be 40 grams per day, which (× 6.25) means the destruction of 250 grams of dry tissue protein. This really means the loss of over 2 pounds of intact tissue protein, such as muscle.

These figures explain why a tremendous loss of weight may occur with great rapidity in diseases in which the loss of protein becomes excessive.

Vitamin Needs. We know relatively little as to the increased vitamin needs in disease. Such knowledge undoubtedly will be forthcoming as further study reveals vitamin metabolism under various conditions.

The requirements for thiamin are known to be dependent upon glucose metabolism By analogy, any condition in which more calories, in the form of carbohydrate, are required will probably also require more thiamin. The modern industrial processing of foods often separates the vitamin B complex from its natural union with carbohydrate in whole grains and plants, so that nature's effort to insure automatic proportional ingestion of these two nutrient elements is frequently thwarted. In the Orient, the use of polished rice led to the recognition of beriberi as a deficiency disease and to the discovery of the B vitamins As might be expected, the intake of thiamin may be greatly reduced if the diet is rich in fat, but low in carbohydrate This is explained by the fact that cocarboxylase, a thiamin complex, is needed for carbohydrate, but not for fat metabolism.

In the sudden and drastic alteration in metabolism occurring with rapid regulation of severe diabetes, signs of thiamin deficiency may appear (leg pains, reflex changes, peculiar mental symptoms) Such symptoms are a reflection of the sudden shift from fat to carbohydrate as the chief source of energy, the need for thiamin suddenly becoming very great and exceeding the supply, and the whole process being accelerated by the frequent use of large doses of insulin

In fevers and in hyperthyroidism there is a general increase in metabolic demands; as a rule, these are largely supplied by increasing the carbohydrate intake Signs of thiamin deficiency may appear if the supply of the vitamin is not increased at the same time

The amounts of thiamin required in the various diseases are difficult to estimate exactly, but from the practical point of view the precise need is perhaps not so important, since it is easy to meet even tremendously increased requirements by the simple expedient of giving large, repeated doses. Between 0 5 and 1 mg daily per 1,000 calories is needed for prophylaxis, while about 10 times such doses, given orally or parenterally, are advisable if there are signs of deficiency

Vitamin C requirements may be increased tremendously in certain sur-

gical conditions. There is definite evidence that large amounts of vitamin C are utilized or destroyed in extensive inflammation, for example in postoperative conditions and burns. The evidence is based upon the fact that this vitamin frequently disappears from the plasma following injury, even though the tissues were saturated with it beforehand. Moreover, it has been observed that very large doses of ascorbic acid, as much as 1 gram or more per day, may be required if the normal level is to be maintained in such cases. The explanation of the high concentrations of vitamin C observed in operative sites may be that large amounts of this vitamin are mobilized when needed at the site of inflammation. The beneficial influence of large doses of vitamin C on wound healing may be associated with this phenomenon.

Prevention of Nutritional Deficiencies in Disease

Armed with a knowledge of the normal nutritional requirements and an understanding of the increased requirements during disease, the physician is in a position to prevent any nutritional deficiencies in a patient who comes under his care at the beginning of an illness. This desirable attitude of prevention cannot be emphasized too strongly Many nutritional problems in disease develop under the very eyes of the attending physician, sometimes advancing to a very severe stage before his attention is directed to the problem. At such a late stage, treatment becomes difficult or even impossible On the other hand, attention to the nutritional requirements from the very beginning would not only avoid a more serious problem later, but would undoubtedly facilitate treatment of the disease itself. In other words, maintenance of a good nutritional status can shorten the course of the disease and eliminate many of the complications which are now known to be associated with various types of nutritional deficiencies

Practices That Lead to Malnutrition. Practices that may cause malnutrition should be avoided; if the nature of the treatment makes interference with normal nutrition inevitable, other means of meeting the nutritive needs must be employed Some of the ways in which medical or surgical therapy may cause serious nutritional disturbances are:

(a) *Therapeutic diets* Diets for allergic conditions, by eliminating certain important foods, especially milk, eggs, wheat, or citrus fruits, may cause deficiency of calcium, protein, B complex, or vitamin C, as well as other deficiencies. Diets for digestive disorders, such as peptic ulcer, colitis, or gallbladder disease may exclude essential nutrients Sippy diets, consisting solely of milk and cream, will lead to iron and vitamin C deficiencies Diets for diabetes often exclude adequate amounts of the B

complex, while diets for obesity may limit vitamins A and D (butter, etc.), B complex (bread, etc.), C (citrus fruits), protein (meat). Very high carbohydrate diets, given orally or intravenously, for liver disorders, etc., may greatly raise the need for the B complex group, especially thiamin. Low protein diets in nephritis may increase the protein deficit already present. Excess fluid intake, if long continued, will wash out vitamins and cause a deficit (as in urinary tract infections or prolonged fevers).

(b) *Physiotherapy.* Such therapy may raise the requirements for all nutrients: hot baths, fever therapy, exercises, and the like. Prolonged rest indoors may cause vitamin D deficit.

(c) *Medication.* This may increase metabolic demands and possibly precipitate nutritive defects. With parenteral glucose therapy large amounts of thiamin should be given and probably also of nicotinic acid and riboflavin. Sulfonamide compounds used in the treatment of bacterial infections exert their bacteriostatic effect by competing with the essential metabolite *p*-aminobenzoic acid for an important enzyme site in the bacterial cell, and also perhaps in body tissue cells, thus preventing the body from utilizing this vitamin. Sulfonamides also destroy bacteria in the bowel; some of these bacteria are important because of their normal function of supplying, by biosynthesis, part of the body's needs of certain vitamins, such as nicotinic acid or biotin (13). Therapy with desiccated thyroid elevates the metabolic rate and thus increases the demand for calories, protein, calcium, and vitamins. Mineral oil used for constipation may, if long continued, interfere with the absorption of fat-soluble vitamins A, D, and K. Alkalis will destroy ascorbic acid and thiamin in the stomach. Neoarsphenamine therapy lowers the plasma ascorbic acid. Sedatives inevitably decrease food intake; large doses, especially of soporifics, usually produce profound anorexia.

(d) *Surgical Procedures.* These may result not only in blood loss, nitrogen loss, vomiting, or anorexia with resultant limited intake of essential nutrients, and loss of vitamin C at the wound site, but in negative calcium and nitrogen balances when there is enforced or complete rest or immobilization in a cast. Operations on the gastrointestinal tract, especially gastric resections, extensive resections of the small intestine, and colostomies, may produce a macrocytic anemia similar to pernicious anemia.

Responsibility for Preventing Malnutrition. The physician cannot shift the responsibility for malnutrition in disease. If he believes that he meets the responsibility by ordering a high protein, high calory, high vitamin diet and by frequently calling in the dietitian to explain the importance of an adequate nutritional intake, he commits a common error. The

dietitian co-operates fully by providing such a diet, and the patient co-operates by consuming as much of the diet as he can. In most cases, however, unless special precautions are taken, no one actually knows how much of this excellent diet the patient has consumed, since the trays are carried away by untrained personnel and no record is kept of the unconsumed food The statement of the patient in such cases is usually unreliable. Under these conditions, the physician is under the illusion that he is paying sufficient attention to the patient's nutritional requirements and is eventually surprised to see malnutrition becoming more and more pronounced. In a thorough study by Stevenson *et al.* (23) it was found that in a large army hospital in Canada the food actually consumed by convalescent patients was less than half of their needs.

Combating Anorexia. The first step in combating anorexia is the recognition by the physician that anorexia is a symptom, to be treated along with other clinical manifestations It cannot be accepted as an excuse for malnutrition The patient's desire for food is not an adequate indication of his nutritional needs.

A laissez-faire attitude toward malnutrition in disease has been responsible in the past for considerable delay in the correction of many deleterious conditions. One should not accept as justifiable any situation just because it occurs in the natural course of events. The harm caused by malnutrition is now so well known that no one can excuse its development on the grounds just enumerated. Only if the administration of food is not followed by its assimilation can starvation be justified This predicament is rare, usually such starvation is only partial. Therefore, adequate supply of protein, calories, and some vitamins should be assured by supplying these nutrients in generous amounts, even in cases (e g., in nephrosis or in parenchymatous liver disease) in which it has been demonstrated that the hypoalbuminemia responds poorly to oral or intravenous protein therapy, or that vitamin K is poorly utilized. As long as the patient shows any evidence of utilizing nutritional elements, the beneficial effects from their administration must be sought by supplying them. Measures should be taken, then, to see that an adequate intake (by whatever method possible) forms part of the treatment.

Anorexia may be combated by various methods, the most obvious but often the most difficult being the art of cooking. Appetizing preparation of food with attention to the patient's idiosyncrasies, serving the food in small amounts and attractively, persuasion, nursing care, all would fall under this category. Sometimes various psychotherapeutic devices may be used, such as the threat of dire consequences, or, in the case of children, the

setting up of rewards. The influence of example, by exposing a patient with anorexia to patients with good eating habits, especially in a ward as group psychotherapy, is often successful. A resourceful physician assisted by efficient, intelligent nursing and dietetic personnel can often overcome all traces of anorexia, even in very sick patients, and achieve an adequate or almost adequate nutritional intake without any special psychiatric means whatever.

Anorexia may be so great as to necessitate a reduction in the actual bulk of the food consumed by the patient Under these conditions some of the caloric value may be sacrificed, i e , a diet may be devised to contain not 15 calories per pound but 5 or 10 calories per pound. This should be done, however, by sacrificing only calories, not proteins and vitamins The patient will lose weight, but the loss will be limited largely to his adipose tissue and can be made up later without any intervening physiologic impairment. In most cases, patients will drink liquid when they will not chew solid food. The following high protein drink, successfully used at Barnes Hospital, will do much to prevent protein starvation:

Whole or skimmed milk	1 qt.
Skimmed milk powder	135 Gm.
Casec (pure casein)	70 Gm.
Cocoa (or vanilla or other flavor)	20 Gm
Sugar	20 Gm.

This formula makes a volume of 1,600 cc , which can usually be taken during 24 hours in divided doses. It contains 136 grams of protein; the caloric content with a skimmed milk base is 1,200, with a whole milk base 1,550 *

Correction of Acute Deficits. A number of disturbing nutritional deficiencies, particularly in water, electrolyte, and protein can be prevented by the prompt recognition and immediate correction of acute losses Fluid replacement is essential in nutrition Many of the useful measures are fairly well known and are not usually considered under the heading of nutrition However, deficiencies in any of the six nutritional substances cannot be separated from each other, by thinking of them as interrelated, an integrated approach can be achieved

Any patient who before or after he comes under treatment suddenly loses considerable amounts of water, electrolyte, or protein, requires their prompt replacement Whenever possible, the normal route of intake, the gastrointestinal tract, should be utilized When this is impossible or inadvisable, parenteral routes should be employed and saline solution, protein hydrolysates, plasma, or whole blood may be given by injection

* *Protenum, a preparation of similar composition, is made by Mead Johnson & Co*

Practical Aspects in Treatment

General Considerations. The routine practice of giving convalescent patients, successively, first liquid, then soft, semisoft, and finally solid diets is not logical. Sometimes recovery is definitely retarded by failure to give the most nutritious diet as early as possible Whether the diet given should be liquid or solid depends upon the patient's ability to ingest and digest it. Many weak patients take liquids most easily because little effort is involved, while others will retain solid food but vomit or regurgitate liquids The diet program must be individual, not routine.

Based on physiologic considerations, food taken by mouth should be divided into (*a*) food which requires digestion and absorption, (*b*) food which requires absorption only. The former group includes all natural foods, such as whole protein, whether in the liquid form or not, starches, most fats, etc. The latter group comprises water, soluble salts and minerals, dextrose, amino acids or small peptides, and soluble vitamins, most of which are now available and can be used in special cases. Such cases include those in which there is some difficulty in digesting natural food, but in which absorption of completely digested food is still possible In such patients, sparing digestion by administering a pure diet of basic nutrients (amino acids, glucose, fats, vitamins, minerals, and salts), either by mouth or through a nasal tube, may be very advantageous The formula described by Olmsted and co-workers (20) has been successfully used in many cases, especially as a basis for the study of food allergy and in the treatment of patients with typhoid fever.

The use of more or less completely digested protein in the form of amino acid mixtures is the most recent addition to the above mentioned purified diet. It has other therapeutic value, as well, as for example, in the treatment of certain cases of peptic ulcer (14) For this purpose it has the following advantages: (*a*) requiring no digestion, it keeps the stomach and intestines at rest; larger amounts of protein can thus be given and protein deficiencies can be more readily relieved than with whole protein, (*b*) amino acids, being buffers, act as antacids, thus controlling hyperacidity to a considerable extent

The need for assuring good nutrition in the various acute and chronic diseases presents many clinical problems For this reason the various conditions may be divided into the following three groups: (*a*) patients already malnourished at the time they contracted their disease and who therefore require special corrective therapy to overcome the deficiency; (*b*) patients whose disease increases the requirement for certain elements in the diet, particularly when there has been an excessive loss, (*c*) patients

setting up of rewards. The influence of example, by exposing a patient with anorexia to patients with good eating habits, especially in a ward as group psychotherapy, is often successful. A resourceful physician assisted by efficient, intelligent nursing and dietetic personnel can often overcome all traces of anorexia, even in very sick patients, and achieve an adequate or almost adequate nutritional intake without any special psychiatric means whatever.

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Any patient who before or after he comes under treatment suddenly loses considerable amounts of water, electrolyte, or protein, requires their prompt replacement. Whenever possible, the normal route of intake, the gastrointestinal tract, should be utilized. When this is impossible or inadvisable, parenteral routes should be employed and saline solution, protein hydrolysates, plasma, or whole blood may be given by injection.

* Protenum, a preparation of similar composition, is made by Mead Johnson & Co.

as much as possible. The use of high protein drinks or amino acids, as already described, will often permit a much higher protein intake.

Inability to Ingest Food Normally. The easiest and the preferable route for a rapid supply of nutrients during acute or chronic disease is the normal one by way of the gastrointestinal tract. However, frequently the patient cannot take any or enough of the essential food constituents by mouth, for example, because of oral, pharyngeal, gastric, or esophageal lesions, because of nausea or anorexia, or because of weakness, coma, or psychiatric disturbance. When the patient has a normal gastrointestinal tract but is unable to chew or swallow, he may be able to take all of the essential nutrients in liquid form by stomach tube.

Tube Feeding. A small nasal catheter may be passed into the stomach intermittently or the catheter may be left in the stomach for long intervals, the latter being the more convenient. Liquid food may be introduced by continuous drip, but probably a better method is injection at intervals of two or three hours, as spoilage is less likely. Moreover, with intermittent injection the stomach can be aspirated before each injection to make sure that it is empty. This, of course, is important, as gastric retention, and particularly the danger of aspiration, especially in the comatose patient, must be avoided.

Tube feeding must always be looked upon as a temporary procedure and is very seldom indicated for long periods of time. This should be explained to the patient before insertion of the tube. In many instances when it is used because of extreme anorexia, the tube can often be removed after a few days, when many patients begin to take an adequate diet normally.

By means of tube feeding predigested food, notably hydrolyzed protein with an objectionable taste, can easily be administered in large amounts. As much as 400 or 500 grams of hydrolyzed protein per day may be absorbed and assimilated in this manner In extremely malnourished individuals, particularly those unable to absorb whole protein either by mouth or in finely divided form by tube, administration of hydrolyzed protein may be very beneficial Formulas for tube feeding offer no particular problem except that they must, of course, be liquid and not too thick to pass through the small opening of the catheter.

Parenteral Alimentation. The parenteral route must never be used with complacency or without adequate indications When this method of administering nutrients is employed, particular care is necessary to minimize or avoid harmful results. In any event, it should be looked upon as a temporary expedient, really an emergency procedure, designed to restore the patient as quickly as possible to a point where he is able to take his

who are unable to ingest any or enough food, and for whom special methods for insuring an adequate intake must be devised.

Malnourishment at Onset of Illness. To a considerable degree, this is a question of preventive medicine, education of the public, and correction of economic factors so that such nutritional deficiencies may disappear. These measures fall beyond the scope of the present discussion.

For the patient with a history of poor nutritional intake and perhaps even with clinical evidence of such deficiencies, the treatment is straightforward, offering difficulties only when food cannot be taken by mouth In such a case the problem is similar to that described under the third group.

Diseases That Increase Nutritional Requirements. In this group must be included deficiencies produced by loss of fluids; these may be water alone, water and electrolyte, or water, electroyte, and protein or whole blood. Such acute losses come under the heading of dehydration and surgical shock, and require immediate replacement by an appropriate type of solution, nearly always by the parenteral route. Aside from these well-known acute deficits, the needs for energy will be increased in hyperthyroidism and in patients with fever or cancer, although much of these needs can safely be met by utilizing adipose tissue. In various infections the need for vitamins, notably ascorbic acid, will also be increased. Normally, not more than 100 milligrams per day of ascorbic acid need be taken, but after severe injury, particularly burns, and after severe abdominal operations, these needs may be increased and an intake of 1 gram per day may be required in order to prevent depletion. More thiamin is undoubtedly needed whenever there is an increased metabolic rate Extra thiamin should therefore be given whenever extra glucose is administered Riboflavin and niacin probably should be increased along with thiamin, since they are closely related to carbohydrate metabolism

Protein needs are increased whenever there has been an actual loss, as already mentioned, due to albuminuria, hemorrhage, or exudation and discharge from wounds Extra needs are also produced by the phenomenon known as the toxic destruction of protein, which may amount to as much as 200 or 300 grams a day. While there is some question as to whether the individual assimilates protein during such a catabolic phase, most clinical observation has shown that there is some advantage in maintaining the protein intake above that usually considered normal If the patient is destroying 200 grams of protein a day, one should try to increase the intake up to 100 grams at least, and perhaps to 150 While it may be impossible to correct all of the protein loss, one should strive to minimize it

Water	2,000 cc
Amino acids (as hydrolyzed protein*)	100 Gm.
Glucose	100 Gm
Sodium chloride	4 Gm.
Total calories	800
Vitamins (given separately by subcutaneous injection)	
Vitamin C, usually 0 5-1 Gm (especially after operation or injury) later	100 mg.
Thiamin	about 5 mg
Riboflavin	about 2 mg
Niacin.	about 25 mg

* Amigen, manufactured by Mead Johnson & Co.

hemorrhage, burns, or other acute conditions. It should be emphasized that for such rapid replacement plasma represents but half of the blood and that, when red cells are lost, whole blood rather than plasma should be given. However, when plasma proteins have been depleted because of malnutrition, the use of transfusions as the sole source of protein has been disappointing, largely because the injected protein fails to remain in the circulating blood and leaves very rapidly, apparently in an attempt to replace protein deficiencies throughout the body As a sole source of protein, moreover, plasma transfusions are expensive and inconvenient. Thus, 60 grams of protein administered in this way requires the bleeding of 4 donors (when 500 cc. are obtained from each, yielding about 250 cc. of plasma each), and involves processing Actually, little is known of the metabolic behavior of plasma protein when injected into the blood stream, such lack of knowledge is important in view of the fact that this method of introducing protein food has no counterpart in any normal physiologic process. The intravenous injection of amino acids, on the other hand, represents a physiologic method in that it approximates the normal way in which protein food reaches the cells after entering the blood stream from the gastrointestinal tract. Nevertheless, in nutritional hypoproteinemia one or more ordinary plasma injections or whole blood transfusions are excellent supplementary procedures and will be followed by added clinical improvement. When plasma and whole blood are the only fluids available for the parenteral administration of protein, they should be used in larger amounts and will exert considerable clinical benefit.

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food and fluid by mouth For this reason the most *successful program of parenteral feeding is the one which achieves this result in the shortest possible time.* Moreover, each injection should be as short as possible with safety; *it is seldom necessary to take more than 4 hours out of each 24 for such therapy.* The use of inadequate solutions often leads to prolonged periods of parenteral feeding; all deficits must be met, all nutrients must be given, if the best (and quickest) results are to be achieved

Of the indications for the use of the parenteral route, *the correction of acute deficits* is perhaps the best known and will therefore not be discussed in detail here. Such injections, which include saline solutions, plasma, and whole blood, are usually urgent. They must always be adequate, and their use precedes any formulation of a plan for supplying the ordinary nutritional requirements over a longer period of time.

The parenteral route is indicated for the correction or prevention of *nutritional deficits whenever oral ingestion is contraindicated. In general,* parenteral therapy is advisable for any disease in which vomiting or diarrhea follows the ingestion of food or where gastrointestinal rest is necessary. *A common indication in surgical practice is the preoperative preparation* of malnourished patients unable to eat because of obstruction or peritonitis, as well as the postoperative treatment during the period before they are able to take food by mouth In medical practice, any disease in which vomiting is persistent requires parenteral feeding to avoid starvation

A parenteral diet can now be made up to include practically all of the essential elements (7) This is possible because the basic elements of the diet (as normally produced from foods during digestion) have now been isolated, and nearly all have been prepared in the test tube. All but one group of the basic elements (the fats) are now generally available Some *of the minerals and vitamins which might be desirable for long continued injection* may still be missing, but for the usual short periods it is probable that the absence of the fats and of some minerals or vitamins is of little practical significance. *As used by the authors, the following represents the simplest plan of parenteral alimentation,* requiring merely the daily injection of 2 liters of solution intravenously One liter is given in the morning, one in the afternoon; each requires about 2 hours The solution contains *the essential nutrients in the volumes and amounts given on page 575*

Plasma transfusions are also a means for parenteral introduction of protein. Actually, there are definite indications for the two ways of introducing *protein substance—plasma transfusion* and amino acids—and they should often be used in the same patient Plasma offers an immediate and frequently life-saving method of replacing plasma protein depleted by

Water	2,000 cc
Amino acids (as hydrolyzed protein*)	100 Gm.
Glucose	100 Gm.
Sodium chloride	4 Gm.
Total calories	800
Vitamins (given separately by subcutaneous injection)	
Vitamin C, usually 0 5-1 Gm. (especially after operation or injury) later	100 mg
Thiamin	about 5 mg
Riboflavin	about 2 mg
Niacin	about 25 mg.

* Amigen, manufactured by Mead Johnson & Co

hemorrhage, burns, or other acute conditions It should be emphasized that for such rapid replacement plasma represents but half of the blood and that, when red cells are lost, whole blood rather than plasma should be given. However, when plasma proteins have been depleted because of malnutrition, the use of transfusions as the sole source of protein has been disappointing, largely because the injected protein fails to remain in the circulating blood and leaves very rapidly, apparently in an attempt to replace protein deficiencies throughout the body. As a sole source of protein, moreover, plasma transfusions are expensive and inconvenient. Thus, 60 grams of protein administered in this way requires the bleeding of 4 donors (when 500 cc are obtained from each, yielding about 250 cc. of plasma each), and involves processing Actually, little is known of the metabolic behavior of plasma protein when injected into the blood stream, such lack of knowledge is important in view of the fact that this method of introducing protein food has no counterpart in any normal physiologic process. The intravenous injection of amino acids, on the other hand, represents a physiologic method in that it approximates the normal way in which protein food reaches the cells after entering the blood stream from the gastrointestinal tract. Nevertheless, in nutritional hypoproteinemia one or more ordinary plasma injections or whole blood transfusions are excellent supplementary procedures and will be followed by added clinical improvement When plasma and whole blood are the only fluids available for the parenteral administration of protein, they should be used in larger amounts and will exert considerable clinical benefit

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Nutrition and Nutritional Diseases In the Orient

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Staple Foods of the Native Population

In general, the diet of the native inhabitants of the Orient consists mainly of carbohydrates, with the fat and protein intake remarkably low. In most of the standard diets of the Occident, the relation of carbohydrates to protein and fats, by weight, varies around 4:1:1, that is, about 55 per cent of the total caloric intake is derived from carbohydrates, 14 per cent from proteins, and 30 per cent from fats. In the Orient, however, 80 to 85 per cent—sometimes even 90 per cent—of all the calories are derived from carbohydrates, 5 to 10 per cent from protein, and about 7 to 8 per cent from fats. Even this small amount of proteins is mainly of vegetable origin. The amount of calcium and of certain vitamins is usually small; and since no

TABLE I

AVAILABLE FOOD IN TERMS OF AGRICULTURAL PRODUCTS FOR VARIOUS COUNTRIES IN KILOGRAMS PER CAPITA PER YEAR

Food	Country							
	China	Japan	Java	Philippines	India	British Isles	U.S.A	Netherlands
Cereals, total	223 0	208	153*	130 9	191 8	95 5	153 2	156
Rice	92 9	160	104	94 9			.	. .
Legumes	32 2	17	10 4†		25.9		...	4 7
Root crops	42 2	131	234‡	39 0		100 4	74 6	118
Other vegetables	41 8	45		5 5	31 1	52 5	103.6	58
Fruit	5 5	15		21 0	20 7	52 3	80.3	42
Sugar	1 4	12	7 0	9 4	18 6	42.3	44 1	33
Meat, fish, and eggs, total	9 4	52	6 6	106 9	5 2	94.6	83.3	40
Meat	.	5	1 3	33 4		..	...	.
Fish	..	47	5 3	73 5		. .	.	
Dairy products	. .				39 5	117.8	177.7	267
Other	8 3	5		45 0	6 1	.	23 0	38
Not accounted for	18 2		...	.		...		.
Total	382 0	485	401	356 7	338 6	555 4	739 8	756

* Corn, 49 Kg. † Soybeans, 7 7 Kg; peanuts, 2.7 Kg ‡ Cassava, 199 Kg; sweet potatoes, 34 Kg, potatoes, 1 1 Kg

animal fats are used, the cholesterol intake is practically zero. Table I illustrates these and several other items.

Total Caloric Intake

The amounts of food consumed per capita per year in the Orient are relatively small as compared with those of the West. However, food consumption must be considered in relation to body weight and basal metabolic rate. In the Netherlands East Indies, for instance, the average male Javanese weighs 46.3 kilogram and the average female, 40 9; the basal metabolic rate of the adult Javanese is about 1,200 calories (1). A Javanese, therefore, needs only two-thirds of the calories required by an Occidental weighing 60 to 70 kilograms and with a basal metabolic rate of 1,600 to 1,800 calories Despite the smaller requirement, menu investigations have shown that actual food intake is often insufficient to cover the needs of the individual.

A Javanese farmer weighing about 45 kilograms and with a basal metabolic rate of 1,200 calories, requires 2,400 calories if he works 5 hours per day. But only in 2 out of 7 different areas of Java where diet surveys were made was the calorie intake sufficient In the other 5 areas an insufficient quantity of calories was taken. The average Philippino gets only 2,180 calories instead of the 2,500 he actually needs. In India, where the Institute of Nutrition in Conoor has carried out extensive diet surveys in 80 to 90 different areas all over the country, the results indicate that the calorie intake of at least 30 per cent of the population of India and Ceylon is below the minimum requirements (2) Part of this underfed population, which lives in barren areas without sufficient irrigation, is permanently on the verge of famine

Animal Proteins

The protein content, in general, of the Oriental diet is low and the intake of animal protein is often negligible As may be seen from Table I, the amounts of meat, fish, and eggs consumed per capita in China, India, and the Netherlands East Indies are very small indeed Table II illustrates in greater detail how poor is the intake of animal products in China Whereas in the United States 61 per cent of the protein consumed is of animal origin, in China only 7 per cent and in the Netherlands East Indies only 5 per cent of the protein are derived from animal sources The figures for Japan and the Philippines are much more favorable, as a result of the popularity of fish in these areas. The official statistics on the meat and fish consumption in the Philippines may be too optimistic It does not seem probable that

the average intake of meat, fish, and eggs in these islands would amount to 106 kilograms per capita per year (3). If this figure were correct, the incidence of beriberi could not be as great in the Archipelago as it actually is. As a matter of fact, other statistics indicate that the Philippinos eat little meat, and that only at particular seasons of the year—if available. In China, only 1 per cent of the total caloric intake is derived from meat, fish, and eggs; in the Netherlands East Indies this figure is 3 per cent; in the Philippines 7.3 per cent; and in Japan 13 per cent.

TABLE II

CONSUMPTION OF STAPLE FOODS IN CHINA (7)

Food	Daily average, per capita, Gm	Food	Daily average, per capita, Gm
Polished rice	251 2	Sweet potatoes	69 0
		Irish potatoes	29 9
		Pork	18 8
		Mutton	5.2
		Beef	7.5
		Eggs	5.8
		Poultry	5.8
		Fish	1.4

One of the many reasons why the food in the Orient consists mainly of vegetable products may be connected with the overpopulation of many of the regions, which is made still worse because in many instances the soil has become depleted by primitive methods of agriculture and erosion. As a result of the overpopulation, the areas which can be allotted to cattle raising are of necessity extremely limited, since both cattle breeding and fish culture—that is, production of animal food—need much larger surface areas to produce a certain number of calories than is needed for the production of vegetable fat and protein. To assure a sufficient caloric intake, the soil of the overpopulated areas must therefore be reserved almost completely to vegetable crops, and meat necessarily becomes a scarce and expensive nutrient.

Religious factors and food customs also play a role in the determination of a people's diet. For example, in China the food customs and ways of preparing food are centuries old. The Chinese pride themselves on the fact that all the different ways in which food is prepared in the civilized world are derived from their culinary art. As far back as the early Middle Ages, when in the Occident the chief ways of preparing food were to bake bread and roast meat over an open fire, the Chinese already used the same cooking

animal fats are used, the cholesterol intake is practically zero. Table I illustrates these and several other items.

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Fats

In the southern Pacific areas coconut oil is the main source of fat intake. Unfortunately, this oil does not contain vitamin A. Although it has often been stressed that replacement of coconut oil by unbleached red palm oil might solve a part of the problem of avitaminosis A in the Orient, the contention seems rather doubtful. Moreover, the taste of red palm oil is unpleasant to most Oriental palates. In Malaya, for instance, where it is used as a natural fat source, xerophthalmia is frequent enough. Sesame oil and peanut oil are generally used in China while soybean oil is used in Manchuria (5).

Vitamins

Since vitamins A and D are present in animal products only, the intake of these vitamins in the Orient must necessarily be at very low levels. This lack of vitamin A intake is not corrected by the carotin or provitamin A intake which in many tropical areas is satisfactory. It is a dangerous fallacy to assume that under all circumstances the vitamin A requirement can be covered by the intake of carotin.

Yellow corn, for instance, contains a considerable amount of carotinoid substances which sometimes are considered to be equivalent to provitamin A In the Orient it becomes evident that one cannot identify these carotinoids with vitamin A since there are many areas where, notwithstanding the large consumption of yellow corn, avitaminosis A prevails. This is observed in the Netherlands East Indies (in Java, 40 Kg of corn are consumed per year per capita), and in China. The areas where the severe forms of avitaminosis A, as for instance xerophthalmia, are frequent, coincide with the regions where corn forms the staple food (6) As a matter of fact, most of the yellow pigment of corn is not carotin but so-called zeaxanthin, which is not believed to act as provitamin A. It is also probable that on a practically fat-free diet the absorption of carotin from the intestine is considerably less than on a diet rich in fat At any rate, it is certain that in the Orient the intake of considerable amounts of carotinoids, as present in yellow corn, does not protect against avitaminosis A.

In those areas where whole grain cereals or certain tubers and nuts are staple foods, the vitamin B intake is satisfactory, but in much larger territories avitaminosis B is frequent.

The large amounts of fruits available explain why avitaminosis C is rare in the tropics.

technic that they follow nowadays. They hold that Marco Polo, after having learned the art of cooking in China, divulged his knowledge to the Europeans, and they are therefore convinced that their way of preparing food is far superior to the methods used in the Occident. In their opinion, only the French cuisine approaches their own in excellence.

Most of the Orientals cannot overcome their loathing of dairy products, especially of cheese and butter, which the Chinese disparagingly designate as "cow-oil." Even milk is unpopular in the greater part of the Orient Only in India is the drinking of milk widespread (2) Here buffalo milk is taken in contrast to the other Oriental countries in which the carabao is used only as a beast of burden. The total annual production of milk in India allows a daily consumption of 6–7 ounces of liquid milk per capita. About 54 per cent of the milk consumed is cow's milk, 43 per cent buffalo milk, and 1.6 per cent goat's milk. The milk of Indian cows contains 25 to 50 per cent more fat than European milk, while buffalo milk contains even twice as much. However, the amount of buffalo milk consumed as such is small, for some 60 per cent of it is used for the manufacture of ghee, a clarified butter. The butter is heated, the supernatant fat is poured off, allowed to congeal, and sold. Only the "buttermilk" which remains after this removal of the fat is consumed by the peasant producer. In the northern, wheat-eating provinces the consumption of milk is higher than in the rest of the country Thus in the Punjab the daily per capita milk consumption is up to 19 7 ounces, but in the Madras Presidency it is only 3 6 ounces. In general, milk consumption in India is a prerogative of the middle class and the rich, the poorer classes usually cannot afford to buy milk

Eggs, one of the other protective foods, are generally liked Unfortunately, their price is often prohibitive In the Dutch East Indies and in Malaya, ducks' eggs are a popular food (4) The indigenous chickens in this part of the Orient lay poorly and the eggs are small. The importation of Occidental types of chickens rarely succeeds because such strains are acutely susceptible to avian diseases to which they become exposed for the first time in this region There are, however, hundreds of thousands of domesticated ducks—the so-called penguin ducks—whose name is derived from their erect, penguin-like posture They are not related to the penguins. These penguin ducks roam all over the island of Java, feeding on the rice fields after the rice has been harvested At night they are driven into flimsy enclosures made of bamboo screens In the morning the eggs which they have laid are collected, after which the flock is released to continue its peregrination to other rice fields Often the eggs are stored for a considerable time in salt and wood ash, or in salt water in large jars.

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The large amounts of fruits available explain why avitaminosis C is rare in the tropics.

TABLE III

STAPLE FOODS CONSUMED PER CAPITA PER DAY* IN CHINA (7)

Province	Food, in grams										
	Polished rice	Wheat	Millet	Corn	Kaoliang (broom-corn)	Soy-beans	Barley	Oats	Proso millet	Sweet potatoes	Irish potatoes
Chahar			297.4		50.5						184
Suiyuan		82.7	82.2					225.5	183.0		274.0
Ningsia	95.3	144.2	59.4						115.8		68.2
Tsinghai		211.5					268	70.1			115.2
Kansu		229.8	82.2	71.2			63		53.6		80.1
Shensi	53.8	340.5	95.6	123.0							
Shansi		181.5	220.0	99.0	96.0			58.0			138.5
Hopei		102.2	253.0	232	167					72.8	
Shantung		153.0	166.0	146	253	101				95.6	
Kiangsu	336	120.5		71.7			73.7			68.6	
Anhwei	389	128			60.2					67.0	
Honan		270	146		135.2	50				98.6	
Hupeh	412	72.7									
Szechwan	478										
Yunnan	475			50							
Kweichow	432			144							
Hunan	570									59.8	
Kiangsi	566									63.2	
Chekiang	522									67.2	
Fukien	511									207	
Kwangtung	506									173	
Kwangsi	497			52.5						57.5	

* Consumptions of less than 50 grams per capita per day have not been listed.

Staple Cereals

There are different carbohydrates which serve as staple foods in the tropics. Most commonly used are:

Rice	Soybean and other legumes	Sweet potato
Corn	Sago flour	Coconut
Millet	Cassava (manioc, tapioca) flour	Wheat

Here again, food customs are important. The cereal eaten in one part of a country may be completely different from that eaten in other parts of the country. For example, in the western part of the Dutch East Indian Archipelago rice is the chief cereal, although there are many areas where *there is considerable consumption of corn and cassava. In the central part,* corn is an important staple food, whereas in the Moluccas and other islands of the Malayan Archipelago and in New Guinea, the population covers the larger part of its caloric requirement by eating sago. In China the differences in staple foods are also very great (Tables III and IV). In northern China wheat, corn, and millet are the staple foods, as well as considerable amounts of soybeans (daily per capita consumption about 30 Gm. in Hopei and Kiangsu, about 100 Gm. in Shantung) (7) Soybeans are also eaten in the south (chiefly in the form of soybean sprouts), but in smaller quantities. Here, rice is the main nutrient Central China and part of south and southwestern China consume large amounts of wheat and rice There are several provinces in China where sweet potatoes form one of the staple foods of the poorer population (daily per capita consumption in Kwangtung and Fukien 173 and 207 Gm , respectively). In several provinces of northern China, Irish potatoes are one of the staple foods (daily per capita consumption 184 Gm. in Chahar, 274 Gm. in Suiyuan, 115 Gm. in Tsinghai, 138 Gm. in Shansi). Considerable quantities of oats are consumed in Suiyuan, as well as in Tsinghai and Shansi.

TABLE IV

AGRICULTURAL GROUPING OF THE PROVINCES OF CHINA

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In the eastern and southern parts of India rice is the staple crop, in most of the northern and northwestern parts rice is replaced by wheat (3). Barley and corn are important crops in the United Provinces in northern India, whereas in the extreme southwest, in Travancore, cassava is one of *the staple foods.* The same holds true for sweet potatoes in Bihar.

Each of these cereals has its own advantages and disadvantages. No discussion of the caloric value of these staple foods is necessary, because most of these carbohydrates, if taken in sufficient amounts, provide a satisfactory caloric intake. These nutrients, with the exception of sweet potatoes and coconuts, consist of about 70 per cent of carbohydrate. Therefore, the 2,400 calories required by the inhabitants of the tropics who work *for their livelihood can easily be provided if 800 to 850 grams of one of the* carbohydrates are taken daily. This holds true even for cassava and sago, which when fresh contain much less carbohydrate, but which are only eaten after they have been dried and made into flour. The protein, mineral, and vitamin (thiamin, carotin) content of these different cereals varies considerably, so that a brief discussion about each one of them is in order (8).

Rice. Rice contains 7.5 per cent of a valuable protein which, especially if mixed with soybean proteins, has a high biologic value Ample amounts of vitamin B_1, minerals, and even fat (1 to 2 per cent) are present in the outer layer of the rice; rice is therefore an excellent food as long as it is only partially milled. Highly polished rice is just as excellent a calorie provider *as unmilled rice, but is completely devoid of vitamin* B_1. *The following* terms are used to designate rice in different phases of processing: (*a*) Paddy or rough rice: 100 per cent of the original weight. (*b*) Brown or dehusked rice 80 per cent of the original weight. (*c*) Farmers' hand-pounded rice: 73 per cent of the original weight, equivalent to about 50 per cent polishing. (*d*) Silverfleece rice: dehusked, but not milled. (*e*) Partially polished rice (as used in Japan): 68 per cent of the original weight, equivalent to about 70 per cent polishing. (*f*) Polished rice: 60 per cent of the original weight.

Table V shows the losses of vitamin B_1 *involved* in the processing of rice.

The reason why such large amounts of rice are milled and polished when *silverfleece rice is such an important protective food is that completely* milled rice can be stored, while silverfleece rice cannot. The vitamins and the fats of the rice are in their highest concentration in the superficial layer, just below the silverfleece. As these substances are excellent foods for [illegible] insects, it explains why silverfleece rice easily becomes rancid [illegible] within three weeks. Silver- [illegible] be eaten by a rural popula-

TABLE V

INTERNATIONAL UNITS OF VITAMIN B_1 PER HUNDRED GRAMS OF RICE (8)

Condition	Dehusked, unmilled (silverfleece)	Half-milled and hand-pounded	Milled and strongly pounded
In original condition	80–125	50–80	20–40
After washing	50–60	25–40	20
After steaming	.	50–80	20–40
After washing and steaming	about 50	15–25	20
After boiling and evaporating		50–80	20–25
After long washing	..	20	20
Parboiled	60–100		
Rice bran (coarse)	200–600		
Rice bran (fine)	600–1,000		

tion which harvests its own rice and eats it within a short time after harvesting. Many of the areas are not self-supporting as far as rice is concerned, and import their rice, usually from the three largest rice-exporting countries—Indo-China, Thailand, and Burma. As all the rice exported from these countries must necessarily be milled, it is impossible to feed the whole rice-eating population of the world only with partially milled, silverfleece rice

Parboiled rice is a popular food in India. This parboiling consists of softening the unhulled rice in water, followed by a short steaming. During this process vitamin B_1 and minerals become diffused through the whole grain and no longer remain concentrated in the outer layers. When the parboiled rice, after drying and dehusking, is milled, only a small fraction of these valuable substances is lost. It has been difficult to popularize this parboiled rice in countries outside India because the finished product has a peculiar taste. Different modifications of the original process have been used to improve the taste Acceleration of the parboiling seems to be an advantage. Nowadays the metal vessel filled with rice is first sucked free of air, and then steam under pressure is introduced during 30 minutes. Thereafter, the rice can be dried, hulled, and milled.

Rice contains other vitamins in addition to vitamin B_1 The vitamin E content is satisfactory, the vitamin B_2 content is low, but the vitamin B_6 content is high.

Corn. Corn contains 9 per cent of valuable protein and sufficient amounts of vitamin B_1. However, corn also must be milled and washed and these processes are instrumental in abolishing the vitamin B_1 content. In some areas corn, after being dehusked, is pounded by hand and then prepared together with the bran. This of course safeguards the vitamin B_1

intake, but this special way of processing corn is limited to a few islands. Old corn is very hard and does not soften easily during preparation. In order to facilitate its preparation, old corn is often boiled with lime, a procedure resulting in a complete loss of vitamin B_1. Of the other vitamins, *corn contains satisfactory amounts of vitamins B_2 and B_6, but the nicotinic acid is very low.*

Millet. This cereal, which is not a popular food in many of the tropical areas, contains about 9 per cent of valuable protein; its great advantage is that it is eaten as a whole-grain cereal, thus providing a considerable amount of vitamin B_1. Millet does not contain much calcium. It is extensively grown in most provinces of India and in the northern provinces of China, where it forms one of the important staple foods. In China millet is eaten mainly by the poorer man, and is looked down upon by the rich—the eating of millet does not give much "face." In some circumstances this lack of appreciation of millet proves to be a distinct advantage. The poorer the inhabitant of northern China, the more millet he must eat, that is, the more whole-grain cereal he ingests and the less chance he has of developing beriberi! If he is very poor, he cannot even afford to buy millet and has to eat *kaoliang* or broomcorn which is also a whole-grain cereal. In this way, the poorest people in northern China are usually well protected against beriberi.

Soybean, Peanut, Mung Bean, and Other Leguminosae. The remarkable qualities of the soybean have been strongly emphasized in recent years and the importance of this legume in nutrition is generally realized. This is especially true of the Orient, where it provides, apart from carbohydrate, large amounts of protective substances in which other ingredients of the Oriental diet are deficient. Soybean flour consists of 35 to 45 per cent of a high-grade protein and 12 to 19 per cent fats, it contains considerable quantities of calcium (0 4 per cent) and of vitamin B_1, all four highly necessary but rare ingredients of the diet of the Orientals. The nutritional problems of a population subsisting mainly on vegetarian foods are greatly simplified if a sufficient quantity of soybeans is added to its diet Unfortunately, soybeans are relatively expensive, compared with the other carbohydrates at the disposal of the Orientals. This unfortunate circum-

composed either of 60 parts corn flour and 40 parts millet, or of 80 parts corn flour and 20 parts soybean flour As soon as the financial condition of the population deteriorates, the flour mixture containing soybean flour

changes for the worse. The price of the mixture does not change too much, but the amount of soybean flour diminishes, that of corn flour increases. As a result, during economic depressions the population does not get enough of the protective foods contained in the soybean.

Soybeans are eaten in the whole Orient. In northern China much larger quantities are eaten daily than in southern China (Table III), but even in the south the people eat soybean products as long as they can get them, especially in the form of soybean sprouts. In the Netherlands East Indies legumes are an important part of the diet. Menu investigations showed that in some places 16 5 to 23 per cent of the proteins of the food consumed were derived from legumes, while 50 to 60 per cent came from rice. In this area not only soybeans but also other legumes, such as mung beans and peanuts, are taken in considerable quantities, forming valuable additions to the carbohydrate diet. One disadvantage of the soybean is its bitter taste. In northern China this is overcome by mixing the soybean flour with other flours. In the Netherlands East Indies soybeans are fermented with molds before they are eaten. Even if the fermentation product, which is called *tempé kedelé*, does not look appetizing to Western eyes, it tastes well. To prepare this dish, soybean mush is inoculated with a tiny particle of a *tempé kedelé*, saved from a previous occasion, and the mass packed in banana leaves. Thanks to the humidity of the tropical atmosphere, fermentation sets in readily. These *tempés* have the great advantage of being easily digested, and their 20 per cent protein content is more rapidly and more completely absorbed than the proteins of the original soybeans. An analogous fermentation process of peanuts leads to the formation of so-called *ontjom*, containing 20 per cent protein and 3 to 9 per cent fat, both of which are much more readily absorbed than the proteins and fats of the original peanuts. Comparable fermentation products are also used in Indo-China and Surinam (Dutch Guiana, in the northern part of South America) The Javanese who emigrated to Dutch Guiana in large numbers brought their *tempés* with them and now continue this processing of soybeans and peanuts.

Soya sauce—popular all over the world—does not contain vitamin B.

In the Dutch East Indies, mung beans are eaten in large amounts. For three hundred years they have been known for their prophylactic influence against beriberi (9).

In India, such peas as the *Cajanus indicus* and *Cicer arietinum* (or chickpea) are valuable supplements to the cereal diet, and play the role which soybeans have in other parts of the Orient. The average consumption of pulses in India varies between 0.5 and 1.5 ounces per day per capita.

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campaign succeeded only too well, and eventually the cassava harvest of Java was so large that about 200 kilograms of this dangerously poor tuber (70 per cent of which is water) was available per year per capita.

Remarkably enough, the leaves of the cassava plant contain considerable amounts of protein (8 2 per cent), and even 1.2 per cent fat and 3 per cent digestible carbohydrate. In the Netherlands East Indies these cassava leaves are eaten as a vegetable soup (*sajoer*), which compensates to a small extent for the low protein content of the cassava flour.

As mentioned above, cassava is also one of the staple foods in Travancore, in southwestern India However, in normal times even there the diet of the poorer classes is not based purely on cassava flour, but on both rice and cassava.

Sweet Potato and Other Tubers. Sweet potatoes, taro, and other tubers which are not washed before they are prepared are qualitatively a much better food than cassava and sago They contain vitamin C and fair amounts of vitamin B_1 The red variety of sweet potatoes is also rich in provitamin A On the other hand, these tubers need much better soil than cassava, and they cannot be stored Although their caloric value is not very high, a population which uses these tubers as a staple food is usually healthier and stronger than a population living on cassava or sago. On some of the Mentawei Islands off the western coast of Sumatra, sago is the main source of caloric intake, and here beriberi is frequent. On other islands of the same group, such tubers as taro and yams are eaten, and the population of the latter islands is completely free of beriberi.

Coconut. The populations of many islands in the central Pacific (Gilbert, Ellice, Tokelau, Marianas, Carolines, Palau, Christmas, Johnston, New Hebrides, New Caledonia, Samoa) and of a few tiny islands in the Banda Sea in the Malayan Archipelago live almost exclusively on coconuts. For well-being and health, such a diet must be supplemented with animal food, usually fish and game

In some areas of Java a fermentation product of the press cakes of coconuts (*bongkrek*) is a popular food *Bongkrek* contains 7 to 14 per cent protein and 1 to 6 per cent fat Whereas [illegible]

specific organism, *Bacillus cocovenenans*, in the fermenting coconut press cake (11), are not rare This intoxication is especially frequent in some districts in the southern part of central Java.

Wheat. Although in many tropical areas only negligible quantities of wheat are eaten, it is a staple food in the northern provinces of India,

Sago. Sago flour is prepared from the marrow of the sago palm. As the marrow is first washed and then dried, the sago flour ultimately contains practically nothing but carbohydrates, with mere traces of protein and vitamins. In the eastern part of the Dutch East Indian Archipelago, that is, in the Moluccas and in New Guinea, sago flour is the staple food of the population. The Alfurs of the Moluccas and the Papuans of New Guinea supplement this sago diet with animals caught in the forest, ranging from small game to caterpillars and larvae. These animals, high in vitamin B and protein, form the necessary addition to the sago flour diet. In New Guinea, the Papuans put maggots into the marrow of a living sago palm, and the opening through which the maggots are introduced is closed carefully. Every morning the Papuan auscults the inoculated area; only when the noise of the growing maggots is loud enough, is the tree opened again. The large maggots are eaten as a delicacy. As long as these tribes remain in the virginal forests their health is relatively satisfactory. As soon as civilization takes hold of these natives, the animals of the forests are despised and deficiency diseases appear.

On some of the Moluccas the sago diet is supplemented by fish and certain nuts, especially the Java almond, which contains much protein and fat.

Cassava, Manioc, or Tapioca. Cassava flour is made from a tuber which can be grown on poor soil unsuitable for rice. Another attraction of cassava is its high yield: eight tons of cassava are raised on the same area from which one ton of rice can be harvested. Finally, cassava needs little care, in contrast to rice which requires continuous supervision—it is a lazy man's harvest. The combination of these characteristics probably explains why the use of cassava as a nutrient is so widespread and why it is a staple food not only in many parts of the Orient but also in certain regions of Africa and of South America. Unfortunately, cassava has many disadvantages (10). The tuber usually contains considerable traces of hydrocyanic acid which has to be removed by washing the flour carefully before it is dried. This washing carries away most of the protein content, low to begin with, of the cassava roots. Thus, the protein content of cassava flour does not exceed 1 to 2 per cent, the fat content 0.2 per cent, while the mineral and vitamin content are negligible. In the cassava areas the protein intake often goes down to 20 grams daily per capita, and hypoproteinemia, hunger edema, and other nutritional deficiencies are frequent in these areas.

Decades ago, when the main problem of nutrition was considered to be the consumption of sufficient amounts of calories, cassava culture was warmly propagated in the Netherlands East Indies, as a solution for the difficulties of nutrition in less fertile areas. Unfortunately, this cassava

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as the general nutrition is satisfactory, but as soon as a carrier becomes underfed, the disease becomes serious Therefore, an improved nutrition of the population is of paramount importance in the campaign against ancylostomiasis. Its incidence among a population has in the long run never been influenced as long as the treatment was limited to repeated worm cures. There are, on the other hand, many examples which illustrate the influence of nutrition upon ancylostomiasis and other diseases. In this connection it should be mentioned that children receiving good food in districts highly infested with hookworm and malaria have a better physique than children in districts where these diseases have only a low frequency but where the nutrition is poor.

The high infant mortality in the Orient is partly due to poor nutrition. The badly nourished children have no resistance against malaria, dysentery, whooping cough, and other communicable diseases. In beriberi areas, infantile beriberi takes a high toll, especially among the three to four month old children.

The female death rate in the Orient is unfavorably influenced by the high mortality from child-bearing It is reported that this also is connected with faulty nutrition.

Low Protein Intake

The low protein intake necessarily favors the development of hypoproteinemia In general, the serum protein values even of healthy native Orientals are lower than those found in the West. As soon as poverty sets in, these figures go down to such low levels that hunger edema, so-called epidemic dropsy, frequently occurs

The fact that vegetable proteins contain only small amounts of certain amino acids may also favor the incidence of different diseases in the Orient. Experimental evidence seems to point to a connection between the development of liver cirrhosis and the absence of certain protective amino acids, such as cystine and methionine, in the food As these substances are scarce in vegetable proteins, the Oriental diet may well be one of the causes of the frequency of liver cirrhosis in this area Parasitic diseases are often incriminated as the cause of liver cirrhosis, and in malaria areas or in regions where Clonorchis, Schistosoma, and other trematodes are frequent, this may well be the case However, liver cirrhosis is frequent in northern China, where malaria occurs only sporadically and liver parasites are practically unknown.

The diet is also poor in substances, usually designated as the extrinsic factor of Minot and Castle, which are necessary for blood formation. This

in northern and northwestern China (Ningsia, Tsinghai, Kansu, Shensi, Shansi, Hopei, Shantung), around the Yangtze valley in Honan, and as far south as Kiangsu and Anhwei (Table III, page 582). Even in Hupeh the daily wheat intake, although smaller than in the more northerly provinces, still amounts to 72.7 grams per capita per day.

Diseases Connected with Faulty Nutrition

The data about the nutrients just presented offer an explanation for several characteristics of the diseases found in the Orient. Even the course of diseases which are not nutritional in origin often is modified there by nutritional influences.

Low Caloric Intake

The low caloric, protein, fat, mineral, and vitamin intakes lead to a generally diminished resistance against disease. As chronic undernutrition favors the development of tuberculosis, the spread of this disease in Oriental communities is often appalling. In northern China surveys of students before entering medical school, of applicants for government jobs, and the like have repeatedly revealed that one of every ten seemingly healthy individuals is suffering from active tuberculosis Obviously one cannot incriminate only the food situation Chinese live together in large numbers in small houses. In old-fashioned houses, such as are found in Northern China, all the family members sleep together on one stone couch, the so-called *kang*, which can be heated by a stove placed beneath it. It follows that if even one member of the family suffers from tuberculosis, the exposure of the rest of the household must be extremely high. But even when this and other circumstances are considered, as for instance, a possible hypersensitivity of the Chinese to tuberculosis, the chronic malnutrition must certainly also be an important factor.

The high mortality of the Orientals during epidemics of acute malaria and dysentery is also said to be partly connected with poor nutrition In general, Orientals stand endemic malaria well, often going about with a chronic malaria infection without too much trouble However, as soon as an acute malaria epidemic flares up, the mortality among the underfed Orientals is much larger than among the white people in the same area. Tropical malaria may lead to an incredibly high fatality, as shown by the mortality figures of 400 per thousand recorded many years ago during a malaria epidemic in Cheribon, Java. The same holds true for the mortality during a dysentery epidemic.

Hookworm infestation (ancylostomiasis) is usually not a disease as long

ment the fetus of the osteomalacic mother grows up with an insufficient provision of vitamin D. Thus, the bones of newborn infants of osteomalacic mothers often show on x-ray examination the irregular surface and cupping of the metaphysis characteristic of the rachitic bone. Such rickets of the newborn usually disappears within a few months, i e., as soon as the child is exposed to the sun. These facts explain the contrast between rickets in the Occident and in the Orient. In the Occident rickets is most frequently seen in bottle-fed children between the age of six months and two years. Here, the fetus grows up in the uterus of a mother who is well provided with vitamin D, and the child is born without any signs of rickets. Only after prolonged bottle feeding with milk poor in vitamin D, that is, after six months, may rickets set in. In China, a child may be born with rickets if the mother is osteomalacic, and therefore rickets, and the closely related tetany, are usually observed in the first three months. After the child is six months old, rickets becomes rare because the tots, with only a few rags on, are placed in the sunny court which every Chinese house possesses. Breast feeding in the Orient is no guarantee against rickets and tetany, since the milk of the osteomalacic mother is poor in calcium and vitamin D.

Another group of individuals threatened by the low vitamin D and calcium content of the food are the children living in orphanages, who are commonly kept indoors to be taught all kinds of useful handicraft. In these orphans, who are not sufficiently exposed to sunshine, so-called late rickets at the time of puberty is not rare.

Even in the tropics the sunshine may be insufficient to prevent osteomalacia. Such is the case in India, where the Mohammedan women who carefully adhere to the purdah are threatened by osteomalacia Forbidden by their religion to be seen by men other than their legal husbands, they remain indoors, under these circumstances, even rich women develop osteomalacia In these areas, especially in northern India, better financial standing is of no avail against osteomalacia. On the contrary, in Kashmir the poorest women, who work as boat women and therefore are in the open air the whole day, never develop osteomalacia, although their nutrition is certainly hardly satisfactory (12).

Low Intake of Vitamin A

[illegible]

of provitamin A. Whereas vitamin A is almost completely absorbed from

explains why macrocytic anemia frequently occurs in the Orient (5) even in persons who secrete hydrochloric acid in the stomach, and therefore produce intrinsic factor. Closely connected with this nutritional macrocytic anemia is the anemia of pregnancy, which in many areas of the Orient is so widespread that it forms a serious public health problem. Incidentally, hypochromic anemia is also frequent because the Oriental food is usually poor in iron.

The syndrome of nephrosis, with high grades of cholesterolemia, occurs commonly in China. The possibility has to be considered whether a low intake of high-grade proteins may favor the development of this syndrome as soon as a subacute nephritis sets in.

Low Intake of Calcium and Vitamin D

The low calcium intake in itself is evidently not important While it is true that the average calcium intake is far below the levels which in the Occident are considered necessary for a minimum requirement, rickets and osteomalacia do not occur in the tropics unless the individual is not allowed to profit from the sunshine. The sunshine provides an abundance of vitamin D formation in the skin Although no vitamin D is present in the diet, the vitamin D formed in the skin is sufficient for the absorption of the modest quantities of calcium present in the Oriental diet and consequently for the prevention of skeletal diseases However, as soon as the body is not exposed to sunshine, the Oriental diet leads to avitaminosis D, as is, for instance, evident in northern China where the sunshine is abundant enough to prevent avitaminosis D under normal conditions. Only the women, who have to stay indoors to fulfill their household duties, are often insufficiently exposed to the sunshine so that they do not manufacture the necessary amount of vitamin D in the skin and the absorption of calcium from the intestine diminishes. Especially women in the childbearing age, who lose calcium with each pregnancy, suffer from osteomalacia (5). It should be emphasized that not only the calcium stored in the skeleton of the newborn infants is provided by the mother, but that even larger quantities leave the maternal organism in the milk during the nursing period The length of the breast-feeding period, which in China is often prolonged to two years and longer, is an important factor in the development of osteomalacia.

In small children, avitaminosis D, i e, rickets, is not too frequent in the Orient because they usually live in the open. Since they are scantily clad, they profit from the sunshine This certainly holds true as soon as they are able to toddle around On the other hand, in the osteomalacia areas, rickets of the newborn is occasionally observed During its intra-uterine develop-

often forgotten that Van Dieren's therapeutic solution of the beriberi problem was sound, although his theory as to etiology was fallacious

Although hand-pounded rice is a good protection against beriberi, it is well-nigh impossible to induce all Oriental rice-eating peoples to eat only such rice. In China, for instance, there is a pronounced preference for white polished rice, and the man who has to eat brown, so-called "dirty," rice loses considerable face. No Chinese, therefore, will eat, unless obliged, silverfleece rice, a fact which leads to unexpected results. The poorer farmers have to eat their own, hand-pounded rice and are free from beriberi; while people who are better off can buy polished rice and develop avitaminosis! The same is seen in the Netherlands East Indies, where the large estates employ hundreds of thousands of Chinese laborers. The estates provide these coolies with partially milled, silverfleece rice, and the incidence of beriberi among this group has gone down to a negligible minimum. It is only the Chinese overseers of the estates who occasionally suffer from beriberi; these overseers, earning larger salaries than the laborers, can afford to buy their own rice instead of eating the despised, "dirty," silverfleece rice which the estates put at their disposal. The beriberi of the overseers demonstrates again that in the Orient money does not always lead to better nutrition. It may well be better to live as a poor man on hand-pounded rice than upon the supposedly better class diet in which white rice is the basis. Large areas of India are free from beriberi because the population eats parboiled rice. In other rice-eating parts of India the widespread custom of eating whole grain millet and unmilled wheat provides sufficient protection against avitaminosis B_1.

It has already been emphasized that the difficulties connected with the storage of unmilled or partially milled rice prevent its general use in countries which are dependent upon imported rice.

In the Netherlands East Indies where vitamin B was first discovered and first crystallized, the Dutch Army had to change its policy about silverfleece rice Until 1923, the only rice distributed to the native troops was silverfleece rice (13). However, the tendency of this rice to become rancid, ultimately obliged the authorities to revert to the issue of polished white rice, but additional nutrients containing vitamin B, such as beans, peanuts, eggs, and meat were given at the same time, in order to provide the necessary protective substances Thus, even in countries where the dangers of polished rice are fully realized, its use cannot be avoided. This indicates how difficult it must be to protect from beriberi a poor, rice-eating population, which must import its rice It also explains why in certain areas of the Netherlands East Indies, such as Bangka Island and the east coast of

the intestine except when specific digestive disturbances exist (fatty diarrhea), even healthy individuals may excrete considerable amounts of carotin in the stool. The low fat content of the Oriental diets has an unfavorable influence on the absorption of vitamin A. Thus, avitaminosis A may develop even when a certain amount of carotin is ingested. It must also be stressed that many of the yellow carotinoids have no provitamin A action. This is true, for instance, of zeaxanthin, the yellow pigment of corn As already mentioned, in the corn-eating areas of China and the Netherlands East Indies xerophthalmia and allied ailments are frequent.

Low Intake of Vitamin B

The loss of vitamin B_1 from rice through the milling and polishing process explains the frequency of beriberi in many rice-eating countries, expecially in such areas as southern China and the Philippines, where mainly white polished rice is eaten In large rural areas of India and the Netherlands East Indies, where the population only eats hand-pounded rice, or *gabah* (in Java 88 Kg. per capita per year), there is no beriberi. Only the hard, outer husk is removed when the native women pound the rice in their primitive utensils, the outer layer of the rice proper, the silverfleece, remaining intact The end product, the brownish looking *gabah*, contains enough vitamin B_1 to protect the population against beriberi.

It should be remembered that this observation of the protective influence of the hand-pounded *gabah* against beriberi was made before the vitamin theories of beriberi had developed. A few years before the classic experiments of Eijkman, this theory was defended with great fervor by Van Dieren, a practicing physician in Amsterdam, who had never been in the Netherlands East Indies and had never had any personal experience with beriberi! He concluded, after a critical, historical survey of the literature, that the disease developed when people were fed on white milled rice (13). Although wrong in his contention that milled rice contained a toxic substance, his practical conclusion was correct He decided from his studies of the literature that beriberi did not occur as long as the natives ate hand-pounded rice (*gabah*), and that patients having the disease rapidly improved when fed with *gabah* Unfortunately, Van Dieren was no experimenter, and had to defend his theory by interpreting the investigations of others. His correct conclusions as to therapy were severely criticized by the infectionists. In the ensuing battle of opinions, Van Dieren not only attacked the latter but for many years continued to defend his toxin theory against the new discovery that beriberi was a deficiency disease. Consequently, it is

have values around 100 milligrams per 100 cc, sometimes even less than that.

Pathologists are still speculating on the possibility that the low blood cholesterol of the Orientals might be a genetic characteristic, like the low adrenal and gonad weights and the scanty hair growth. But, already twenty-five years ago Dutch clinicians showed that the low blood cholesterol of the Indonesian is not a racial characteristic. Careful investigation revealed that the blood cholesterol of Javanese serving as waiters on the luxury ships plying between the Netherlands and the Indies reached levels comparable to the average figures found in the Occident

It is obvious that diseases connected with cholesterol infiltration can be expected to be uncommon among Orientals. This may well be one of the reasons why arteriosclerosis is a rare disease in the Orient (5). Although the Electrocardiography Division of the Department of Medicine of Peiping Union Medical College was a very active one, electrocardiograms showing the typical features of coronary thrombosis were rare exceptions in the collection. There were many years when not a single case of coronary thrombosis was encountered. Other afflictions connected with arteriosclerosis were also extremely rare, and though diabetes is a frequent ailment among Chinese, amputations for diabetic gangrene are practically unknown.

Another characteristic of diabetes mellitus in China is the rarity of ketosis Cases of diabetic coma are hardly ever encountered. This is probably due mainly to the low caloric intake, although it may also be connected with the low fat intake

For the sake of completeness it should be added that, although arteriosclerotic gangrene is rare, thrombo-angiitis obliterans occurs rather frequently, another point in favor of the fundamental differences between these two diseases And whereas coronary sclerosis is rare, calcification of the aortic valves, evidently the result of rheumatic infection, is not infrequently met with at autopsy The latter experience indicates that the infrequency of coronary thrombosis in northern China cannot be explained by the relatively short span of life of the Oriental.

Low Incidence of Amyloidosis

The extreme frequency of tuberculosis among the Chinese was noted on page 590. This is true not only of pulmonary tuberculosis (usually with cavitation) but also of lymph gland tuberculosis with fistula formation. Another frequent disease is osteomyelitis, leading to the formation of pus-secreting fistulas which usually remain active for many years because

Sumatra, where the population relies upon imported rice, beriberi does occur. In India, beriberi is frequent only in northeastern Madras, where polished rice is the staple food. In contrast to the rural areas of the tropics, where mainly hand-pounded rice is eaten, in the cities, especially in barracks, prisons, and orphanages, where the inmates must eat polished rice, the danger of beriberi is ever present. In recent years, however, continuous supervision by the authorities has usually succeeded in preventing the development of beriberi.

As rice and many other cereals are poor in vitamin B_2, ariboflavinosis is a widespread ailment all over the Orient.

Intake of Vitamin C

Avitaminosis C, in the form of scurvy, is relatively rare in the Orient, except during actual famines. In northern China even poor people always try to eat some vegetables, and as these have to rely upon turnips and Chinese cabbage, both rich in vitamin C, evidently the intake of this vitamin is usually sufficient to ward off the development of scurvy. In the tropical parts of the Orient, fruits are so abundant that a certain amount of vitamin C is always ingested

Pellagra

Although isolated cases of pellagra have been observed everywhere in the Orient, large outbreaks of this disease have not been recorded Most of the staple cereals contain a certain amount of nicotinic acid, and in the corn areas evidently other supplementary nutrients are taken which prevent the development of pellagra

Advantages of the Oriental Diet

The disadvantages of the low caloric diet of the Orient, with its inadequate amounts of protein, minerals, and vitamins, have been emphasized so often and so strongly that it seems appropriate to consider whether this diet has also some advantages.

Low Incidence of Arteriosclerosis

The absence of animal food restricts the cholesterol intake to a very low minimum. This must be the reason why the blood cholesterol of the Orientals is lower than the values one is accustomed to find in the Occident. Whereas in the United States blood cholesterol values of 250 to 300 milligrams per 100 cc. are customary, in the Orient the values usually range around 150 milligrams per 100 cc Poor coolies in northern China often

the rarity with which amyloidosis develops even in tuberculous Chinese patients.

Low Incidence of Gallstones

In view of the close relationship between cholesterol metabolism and cholelithiasis, it is obvious that the gallstone problem in the Orient must differ from the Occidental gallstone disease. The very much lower average blood cholesterol values in the Orient explain why cholesterol stones do not occur in the Indies and in China. In the West cholesterol stones occur 4 to 5 times more frequently in women than in men, whereas in China gallstones are by no means especially frequent in women. Typhoid and salmonellosis are the prevailing infections leading to gallstone formation; as typhoid and paratyphoid occur more frequently in the male than the female, there is a larger number of male patients with cholelithiasis in China than of female patients.

Another point which has to be considered is the composition of the stones. As inflammatory gallstones always contain considerable quantities of calcium, the gallstones in China are nearly always radiopaque. Chinese clinicians, therefore, are loath to diagnose gallstones which cannot be visualized on an x-ray film.

The hypercholesterolemia of nephrosis, however, does not depend on the cholesterol intake When nephrosis develops in poor Orientals, whose cholesterol intake is practically zero, the serum cholesterol values rise to the same levels as seen in nephrosis patients in the Occident. The hypercholesterolemia of nephrosis is probably related to faulty metabolism.

Suggestions for Improving the Oriental Diet

It has been shown that the purely vegetarian diet of the Orientals has definite disadvantages, but that in other respects it may even be superior to the diet in the West There is therefore no reason to decry the Oriental diet as completely faulty Frugality is dangerous when it is carried to an extreme, but judiciously observed, a restricted diet may well be a safeguard against certain degenerative diseases By certain changes and additions, the diet in the Orient could be so much improved that most of the disadvantages would be eliminated In this connection the following might be worth considering for a future nutritional policy in the Oriental areas.

As explained above (page 579), the Oriental will always necessarily have to subsist mainly on a vegetarian diet, so that one of the main problems is how to provide sufficient and biologically valuable proteins

surgical treatment is rejected. Finally, syphilis with formation of gummas is of common occurrence. Although in the Occident all these diseases are conducive to the formation of amyloid, in China amyloidosis is an extremely rare disease—much rarer than in the Occidental countries. The following statistics (5), illustrate the differences between the Orient and the Occident.

Saleeby found in 3,047 consecutive autopsies in The Philadelphia General Hospital 50 instances of amyloidosis (1.7 per cent), and Rosenblatt in 1,727 consecutive autopsies at Montefiore Hospital, New York, 125 instances of amyloidosis (7.2 per cent). On the other hand, in Peiping Union Medical College only 5 cases of amyloidosis were found in 2,046 consecutive autopsies on Chinese patients (0.25 per cent). In the same hospital 214 consecutive autopsies performed on non-Chinese patients revealed 4 cases of amyloidosis (1.9 per cent).

As amyloidosis nowadays is found principally in patients with tuberculosis, it is important to compare the frequency of amyloidosis in autopsies of tuberculous patients

In 451 autopsies on tuberculous patients in the United States, Rosenblatt found 110 cases of amyloidosis (24.4 per cent); Bornfin in 100 autopsies, 18 cases (18 per cent); Fishberg in 604 autopsies on tuberculous patients, 25.5 per cent. However, in 240 autopsies on Chinese patients with tuberculosis as the major condition or cause of death, only 3 cases of amyloidosis were observed (1 3 per cent) in Peiping Union Medical College Hospital

Of the 5 cases of amyloidosis in Chinese patients observed in the Peiping Union Medical College Hospital, 3 were due to tuberculosis and 2 to syphilis. The diagnosis in the 4 non-Chinese patients suffering from amyloidosis were respectively leprosy, tuberculosis, actinomycosis, and carcinoma of the lung.

One can only speculate about the explanation of the infrequency of amyloidosis in Chinese patients. The supposition that it does not develop in the Chinese because they die more quickly from chronic suppuration than Westerners, is easily refuted by clinical experience The following point may be worthy of consideration Experimentally in animals, amyloidosis develops under different circumstances, one of which is the feeding of an excess of casein or casein-rich food such as milk, cheese, and eggs. In this respect it must again be emphasized that dairy products are completely absent from the North Chinese diet, so that food with a high casein content, such as milk or cheese, is never taken except in certain regions of Mongolia, Kokonor, Sinkiang, and Thibet, and by a small part of the urban population Perhaps there is a connection between these dietary habits and

ciple; it is therefore of great importance for a population whose protein and vitamin intakes are low, and which has a tendency to develop nutritional anemia. Yeast factories, which undoubtedly will have to be government operated, can in the future have an important influence upon the protein intake in the Orient.

Increased Egg Consumption

Orientals like eggs, but the price of eggs is often prohibitive. The fact that the Oriental chickens lay relatively small eggs is not so important as the fact that countries like China export millions of eggs which should really be consumed by the population of China. It will be necessary to devise a policy to keep the eggs in the country.

Increased Fat Consumption

Increase of the fat content of the food will be necessary in order to balance the diet and also to improve the absorption from the intestine of substances like provitamin A. In some areas it would be relatively easy to do so. In the Netherlands East Indies, for instance, where the export of coconut products is stimulated by various government measures, this policy will have to be revised in order to keep a larger quantity of these products within the country The consumption of this valuable fat should be stimulated by reducing its price, perhaps even with government subsidies.

Increased Fish Consumption

Nearly all Orientals like fish While it is practically always available in the coastal areas, the distribution of this valuable food into the interior is nearly everywhere deficient. Improvement of the transportation systems would lead to considerable improvement of the general nutrition.

Production of Shark Liver Oil

It does not seem impossible that in the Orient shark liver oil may become a very important ingredient of the daily diet. It is cheap, and is rich in vitamin A. This material, although devoid of vitamin D, could take the place which cod liver oil has in the West The absence of vitamin D in shark oil is no disadvantage, since the inhabitants of the tropical Orient manufacture their own vitamin D, thanks to the abundance of sunshine.

Popularizing Hand-Pounded, Silverfleece, or Parboiled Rice

In the rice-eating areas, the hand-pounding of the rice by the population will have to be propagated, and where hand-pounding is not practicable,

Popularizing the Soybean

Increased consumption of soybean products will be an important improvement, not only because soybeans are rich in calcium, vitamin B, and proteins, but especially because the soybean protein is biologically valuable. Excellent work has been done in the Dutch East Indies, where the quantity of soybeans available per capita per year in Java has increased from 2 1 kilograms in 1920 to 7.7 kilograms in 1939 (14). Most Indonesians in Java have small gardens near their houses, and among the vegetables cultivated soybeans have assumed an important place. Since a large part of the rural population's food comes from these gardens, the rural folk in the Dutch East Indian Archipelago are often well supplied with soybean proteins. But as soon as laborers' wages are increased and the economic level of the population goes up, the incentive to cultivate the home garden grows less. The man who earns enough money to buy food in a shop, does not think it worth while to exert himself to raise his own vegetables and other food. The useful vegetable gardens around the Indonesian houses are therefore well tended only as long as the financial level of the population remains moderate. The same phenomenon has been observed in Malaya.

The same difficulty is encountered in areas where the population lives from the production of export crops. In the Philippines, for instance, the relatively high income from sugar production—an export crop—has resulted in a neglect of the food crops. It should, however, be stressed that these factors, so important for the nutrition of the rural populations, do not influence the condition of the urban population, since in cities there are no gardens around the houses

A well-planned government policy is essential if the nutrition of the Orientals is to be improved. This policy may well require subsidies to keep the price of the soybean low, for only then will large masses of the population be in a position to buy this valuable product It will certainly be necessary in the Netherlands East Indies and in southern China, where a satisfactory soybean consumption can be instrumental in reducing the incidence of nutritional diseases Even in northern China, where soybeans are a popular nutrient, such a policy will increase the consumption of this legume among the poorer classes.

Popularizing Yeast Consumption

An important source of protein which just started to be developed when World War II began is yeast. Yeast can easily be grown on molasses in all areas where sugar is cultivated. Yeast contains not only a high-grade protein, but also considerable amounts of vitamin B and hematopoietic prin-

Flour: Rice		375	6	1	85	0.036	..	...	..
Corn		335	10	3	67		150	0	..
Wheat	*Triticum aestivum*	345	12	1	72	0.003	+	0-++	0
Potato		331	0	0.3	82	..	0	0	0
Cassava		307	1.5	0.1	75	..	0	little	0
Soybean		436	40	20	24	...		80	0
Sago	*Metroxylon sagu*	341	0.04	0.1	85	...	0	0	...
Groundnut (peanut)	*Arachis hypogaea*	..	25–32	40–50	10–20	0.05	60	300	0
Soybean	*Glycine soja*		35–45	12–19	10–20	0.40	70–130	40–100	4
Mung bean	*Phaseolus radiatus*		19–23	0.2–2	40–60	0.06	150–400	50–400	9
Candlenut (kemiri nut)	*Aleurites moluccana*	650	19	63	1	..	0	20	...
Java almond (kenari nut)	*Canarium commune, C. moluccanum*	660	15	66	3	0.13	0–+	140	...
Coconut, fresh	*Cocos nucifera*	..	4–5	43	2–7	0.018	.	10–20	+
Tempé kedelé (fermentation product of soybeans)		.	±20	±4	±5	0.18	trace	50	0
Ontjom (fermentation product of peanut press cake)			20–30	3–9	±4	0.08	.	60–200	..
Bongkrek (fermentation product of coconut press cake)			7–14	1–6	±3	...	.	...	
Sesame oil		900	0	100	0	...	0	..	...
Red palm oil	*Elaeis guineensis*	900	0	100	0	...	80,000	...	..
Coconut oil		886	1	98	0	...	0	..	...
Soy sauce		...	2–12	0.1	17	...	0	0	...
Yeast		.	57	3	...	...	...	1,500	..

TABLE VI

COMPOSITION OF FOODSTUFFS COMMONLY CONSUMED IN THE ORIENT (8)

Name of product	Botanical name of plant	Calories, per 100 Gm.	Food constituents				Vitamins, I U. per 100 Gm.		
			Protein	Fat	Digestible carbohydrates calculated as starch	Calcium	A	B_1	C
Rice	*Oryza sativa*								
Silverfleece		347	8	2.5	73	0.02	0–+	100–150	0
Half-milled		339	7.5	1.0	75	0.01	0–+	60	0
Polished		343	7	0.3	78	0.01	0	10	0
Parboiled		350	7	0.6	79	0.009	0	25	0
Bran			6–14	3–18	38	1.2	+	200	0
Corn	*Zea mays*								
Nonmilled		320	8	4	63	0.05	0	60	0
Milled			9	1–4	70–78	.	0–+	0–+	0
Bran		.	9	2–15	39–49		0–+	400	0
Great millet (sorghum)	*Sorghum vulgare*	300	9	4	58	0.15	140	60–100	4
Common millet (broomcorn millet)	*Panicum miliaceum*	315	12	5	60	0.01	+	+	0
Cassava, fresh unwashed	*Manihot esculenta*		1	0.2–0.4	30–36	0.05	0	10–100	20
Cassava leaves			8	1.2	4	0.29	5,000	50–100	+
Sweet potato	*Ipomoea batatas*	≈120	0.5–1	0.2–1.8	24	.	0	...	...
Dasheen, taro, green taro	*Colocasia esculenta, C antiquorum, C indica*		2–4	0.2 0.2	35	0.092	...	25–100	+
Yam	*Dioscorea hispida*	71	2	0.3	15	0.02	...	10–20	...
Potato	*Solanum tuberosum*	89	2	0.1	20	0.006	40	30–80	13–15

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15 Statistical Abstract of the Netherlands Indies, 1940, p 142 (Pocket edition)

the consumption of silverfleece rice or parboiled rice will have to be popularized.

Government Regulation

A planned agricultural economy will be necessary in many Oriental areas In the Netherlands East Indies the government has already begun to curtail the production of export crops in special areas and to promote the production of food crops. In such regions as the east coast of Sumatra, restrictions were placed on cultivation of products like rubber and tobacco and the farmers were obliged to employ the land for the growing of food crops.

This compulsory regulation of crops applied only to the islands other than Java. During its short period of operation, between 1939 and the outbreak of the Pacific conflict, it had already led to an increased food production, some 150,000 to 200,000 hectares having been added to the food-producing acreage in the years 1939 to 1941.

Such a policy of compulsory cultivation may well have to be extended to and accepted in other parts of the Orient as well.

There are regions where the condition of the soil makes the problem of obtaining a satisfactory food supply seem well-nigh impossible. Transmigration, that is, the transfer of the population from barren areas to more fertile regions of the Archipelago, has been resorted to in the Netherlands East Indies. This policy, too, may have to be expanded and be used in other parts of the Orient.

If the nutrition of the general population of the Orient is to be improved and adequate food supply assured, extensive government planning will be necessary. Definite policies and programs on landlord–land tenant relations are called for Furthermore, the provision of nourishing food must be considered the duty of the government, just as is the provision of safe drinking water And finally, the nutrition of the population will become satisfactory only when agriculture is no longer directed exclusively toward raising crops which give the greatest monetary reward but toward the growing of products which are vitally necessary for the health of the population.

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